

# THE CANADIAN MEDICAL ASSOCIATION

## LE JOURNAL DE

### L'ASSOCIATION MÉDICALE CANADIENNE

JUNE 3, 1961 • VOL. 84, NO. 22

#### FACTORS CONTRIBUTING TO RECOVERY FROM VIRAL DISEASES\*

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TREATISES on viral diseases provide little information bearing on the recovery process. That recovery from viral diseases occurs commonly is obvious and considered as natural, but the factors that contribute to this remarkable process are either neglected or thought to be too uncertain to merit penetrating evaluation. To judge from publications in scientific journals, it appears that experimental approaches to the mechanism responsible for recovery are rarely undertaken and that relatively little research is stimulated by curiosity about this common and important phenomenon.

It is surprising that this should be so, for spontaneous recovery is the most probable outcome of human viral disease. This fact is clearly recognized by students of these maladies and is thoroughly documented in modern textbooks and monographs. For each of the more than 50 viral diseases of man the prognosis is now fairly well established, and the likelihood that enduring sequelae will develop or that death may occur can be estimated without much error.<sup>1, 2</sup> Even though such estimates may be of small value in the management of individual patients, they serve to define with fair accuracy expectations regarding the course of illness in large numbers of patients.

Recovery is not only the most common issue of human viral disease; it is for many the rule.<sup>3</sup> Most persons have recovered fully from several of the exanthemata of childhood, particularly measles, rubella and varicella, and also have experienced repeated recoveries from a variety of acute respiratory diseases, especially the common cold, adenovirus infection and influenza. Moreover, the majority of human beings have recovered from herpetic stomatitis and mumps. Excepting only rabies, no viral disease of man seems certain to be uniformly fatal.<sup>1</sup> In the great bulk of instances, episodes of human illness induced by viruses lead

TABLE I.—CURRENT ESTIMATES OF THE CASE RECOVERY RATE IN VARIOUS HUMAN VIRAL DISEASES

<i>Viral diseases</i>	<i>Probable case recovery rate</i>
	%
Influenza, measles, rubella, varicella, mumps, herpes simplex, hepatitis, primary atypical pneumonia.....	99 or more
Yellow fever, Western equine encephalomyelitis, psittacosis, poliomyelitis*.....	90 or more
St. Louis encephalitis.....	80 or more
Smallpox.....	70 or more
Japanese B encephalitis*.....	60 or more
Eastern equine encephalomyelitis*.....	20 or more
Rabies.....	0

\*Often with serious and persistent sequelae.

to spontaneous recovery and only rarely lead to enduring abnormalities of physiological function.

Current estimates<sup>1, 2</sup> of the occurrence of recovery from several viral diseases of man are indicated in Table I. Recovery is intended to indicate that the patient survives, that the signs and symptoms of disease disappear and that evidence of physiological abnormalities does not persist unless so stated. Only about five of the diseases identified have case recovery rates as low as 80% or less, while in at least eight diseases, as well as in a number of others, recovery ensues in 99% or more of patients. Serious and persistent sequelae are common only in three, each of which may cause serious damage to the central nervous system. Among human viral diseases, rabies seems to be the only exception, and it appears that in this condition there is no proved instance of recovery in man.<sup>1</sup>

The well-known, though little emphasized, fact that recovery is common in man and most animals becomes surprising when considered in the light of current information on the remarkable mechanism of viral multiplication as well as the associated and often profound alterations in cell function. It becomes astonishing when it is set against the results of viral diseases in insects and bacteria which do not lead to recovery. For the purposes of this discussion, disease is considered to be present when there exists obvious evidence of malfunction regardless of the dimensions or complexity of the infected host organism. A summary of current information concerning recovery from viral diseases in various host organisms is shown

\*Read before The Montreal Medico-Chirurgical Society, Montreal, February 15, 1960.

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TABLE II.—OCCURRENCE OF RECOVERY FROM VIRAL DISEASES AMONG VARIOUS HOST ORGANISMS

Host	Number recovering
Man.....	Very many
Mammals, other than man.....	Many
Birds.....	Many
Insects.....	None
Plants.....	Considerable
Bacteria.....	None

in Table II. It should be emphasized that among the many varieties of hosts on which adequate data are available, only insects and bacteria regularly fail to recover once viral infection has progressed to the point of inducing obvious malfunction. For reasons which will be described below, it seems of considerable importance that plants are capable of recovering from several viral diseases.

One way to approach the problem of recovery might be to ask: What are the factors available to man and most animals which contribute to the recovery process that are either nonfunctional or noncontributory in insects and bacteria? One factor which might qualify as an important contributor is specific antibody which can combine with and neutralize the infectivity of mature virus particles when they are outside of host cells.

In man and animals, viruses are recognized as containing antigens unlike those of the host.<sup>4</sup> Infection with them leads to the production of antibodies specifically oriented to react with the protein coat of the virus particle. In some instances, though by no means in all, the signs and symptoms of viral disease tend to become less striking and the recovery process may begin at about the time that the production of circulating antiviral substances becomes significant. This occasional association in time has led to the assumption of a causal relationship which holds that in man and animals, at least, the antibody response to viral infection may be an important factor in recovery.

Although it has been reported that insects share with other animals the capacity to produce various types of antibodies, recent studies have failed to establish that they develop antibodies against viruses. Viral diseases of insects, like those of bacteria, appear to be uniformly fatal, and the available literature fails to record an instance of recovery after evidence of malfunction has appeared. However, susceptibility to viral disease in insects seems to be confined exclusively to their larval and pupal forms; adults are not affected.<sup>4, 5</sup>

Unlike animals, plants appear unable to produce antibodies, and so, when recovery from viral disease occurs in such species, specific antibodies against the virus can hardly be invoked as contributory. Although viral disease of bacteria, defined as obvious evidence of malfunction, is thought constantly to lead to death of the cell, there are a number of virus-induced diseases of plants in which recovery is known to occur.<sup>6</sup> In some varieties of sugar cane, for example, recovery is so common that mosaic disease is of small consequence. Here, then, are instances in which re-

covery occurs in the absence of antibodies, and, therefore, whatever their role in viral diseases of animals, it would not be consistent with the facts to contend that as a general principle antibodies are important contributors to the recovery process.

Animal embryos and fetuses also are thought not to be capable of producing antibodies. Such as are found in them are believed to be of maternal origin. Chicken embryos developing in the fertilized egg are free of antibodies and are known not to be capable of producing them. Numerous viral diseases can be induced in such embryos with agents derived from man.<sup>1, 4</sup> In some instances, particularly with influenza or mumps virus, recovery may occur, and, on hatching, the chick appears to be wholly normal. Although the number of virus particles present in the embryo a few days before hatching may have been very large, none are found after hatching, and antibodies against the virus do not develop even when the chick matures. This provides additional evidence that the recovery process is not necessarily dependent upon the production of antibodies against the infecting virus.

Nature has provided one of the most telling arguments against the antibody hypothesis in man himself. Patients with agammaglobulinemia appear not to possess antibodies and seem to be incapable of producing them, as has been shown with a variety of antigenic stimuli. Yet such patients, although constantly in jeopardy of recurring bacterial diseases, appear to react as do normal persons to various viral diseases.<sup>2</sup> Varicella, measles, mumps, herpes simplex and vaccinia virus infection have been observed in patients with agammaglobulinemia. In a number of instances recovery has occurred at the expected time, and direct tests have failed to show that antibodies against the viruses were produced.<sup>7</sup> In the light of this evidence, there seems to be little reason to think that antibodies regularly provide a significant contribution to recovery even in human beings.

TABLE III.—HOST ORGANISMS THAT MAY RECOVER FROM VIRAL DISEASES WITHOUT PRODUCING ANTIBODIES

Host	Circumstance
Man.....	Agammaglobulinemia
Birds.....	Embryos
Plants.....	Certain viruses

The facts just described are summarized in Table III. Should further evidence be desired, attention may be directed to the results of attempts to bring about recovery by giving antibodies. As is now thoroughly established, the injection of immune sera containing specific antibodies does not affect the course of viral diseases after definite signs and symptoms have appeared.<sup>1, 2</sup> Regardless of the amount of antibody that is given after the disease has become manifest, the outcome is not altered, and the time at which recovery occurs appears not to be advanced.

In view of current concepts on the mechanism of viral reproduction and the associated damage that may be induced in cells, it would, in fact, be surprising if antibodies were able to affect either process. The mechanism by which viruses are reproduced appears to be unique in biology, for it seems to involve disintegration of the infecting virus particle and the separate synthesis within the host cell of the specific precursor materials that are needed to produce new virus particles. These precursor materials, chiefly nucleic acid and protein, are demonstrably different from those normally produced by the cell. After the new polymers are synthesized, an appreciable time elapses before they are brought together and assembled into mature virus particles which have properties identical to those of the particle that was lost in initiating infection of the cell.<sup>1, 4</sup>

Unlike the multiplication of cells, be they animal, plant or bacterial, wherein new cells arise from the growth and division of older cells, viruses seem to have no continuity as formed elements and are reduced to their molecular components during each reproductive cycle. Because reproduction is wholly an intracellular process, both specific precursor materials and new virus particles are protected from any contact with antibodies, for these substances appear to be unable to enter the living host cell. However, when mature virus particles escape from infected host cells and are temporarily free in intercellular fluid or blood, they are readily affected by specific antibody which inhibits them from infecting other cells. Although this process may prevent systemic spread of the agent and certainly is an important factor in subsequent immunity to reinfection, it seems to have little relevance to the process of recovery from disease.

Spread of virus locally within a tissue may occur through the serial infection of cells closely adjacent to those already infected. The distance between tissue cells is commonly shorter than the diameter of a virus particle which, therefore, may move from one cell to another without ever being wholly outside either. It is no surprise then that antibody is not consistently effective in preventing spread of virus particles between neighbouring cells. This has been particularly well demonstrated with polio-virus infections of the central nervous system in which cell-to-cell spread occurs even when antibodies are present in high titre.<sup>8</sup>

Recently a truly startling fact has been discovered.<sup>9-11</sup> Viral nucleic acid can itself initiate infection even when it is not contained in an intact virus particle. As indicated in Table IV, ribonucleic acid purposely separated from certain plant or animal viruses is infective and after it has entered susceptible cells induces the production of new virus particles. These are in all respects identical to those from which the infective nucleic acid was originally obtained. Thus, it appears that viral reproduction depends upon the stimulus and the information that is provided to the cell by the

TABLE IV.—VIRUSES THAT YIELD INFECTIVE NUCLEIC ACID

<i>Virus</i>	<i>Nucleic acid</i>
Tobacco mosaic.....	RNA
Mengo.....	"
West Nile.....	"
Eastern and Western equine encephalomyelitis...	"
Poliomyelitis, Types 1 and 2.....	"
Foot-and-mouth disease.....	"
Mouse encephalomyelitis.....	"
ECHO, several types.....	"
Coxsackie, Groups A and B.....	"
Polyoma.....	DNA
Phage, T2.....	"

genetic material, the nucleic acid, of the infecting particle. In some instances this specialized material may be produced by infected cells in excess of the amount needed for the assembly of mature particles. When infective nucleic acid escapes from cells in which it originates, it may instigate viral reproduction in other cells. Of most importance, free nucleic acid is not affected by antibodies produced against the intact virus particle and retains full infectivity in the presence of these substances. As a consequence, even in the immune host, virus-infected cells may produce a substance which, when it escapes from the cell, can initiate the production in other cells of more of the same substance. This self-replicating material, the viral nucleic acid, appears to carry in molecular code all the genetic information that is needed for the production of new virus particles in the cell.

Although there are indications that certain antibody-like proteins, such as those recently found in the serum of patients with lupus erythematosus, may react with cell nucleic acids, there is no evidence that similar proteins occur in immune sera that react with viruses. Among substances classically associated with immunity, there appears to be none yet identified which would be expected to interfere with the serial infection of cells in successive cycles by viral nucleic acid.

As has already been stated, viral reproduction often leads to cell damage. If the damage becomes sufficiently marked and if the number of affected cells is sufficiently large, gross evidence may appear in the form of recognizable lesions. Historically it was the development of lesions after the inoculation of cell-free extracts not containing bacteria that led to the discovery of viruses. To this day techniques have not been developed for the unequivocal recognition of wholly innocuous viruses, if such there be, and most viruses are still recognized and identified by procedures which depend largely upon the capacity of these agents to induce cell damage.

Although viral reproduction appears in nature to be a necessary prerequisite for the induction of cell damage, it seems doubtful that it provides a sufficient explanation for the abnormalities that may develop. At the morphological level the evidences of induced cell alteration are neither very numerous nor very complex. As was emphasized

more than 30 years ago,<sup>12</sup> the cell is either stimulated or depressed and sometimes both, in that order. A tissue, composed of a large population of infected cells, may show hyperplasia or necrosis, occasionally both. At the biochemical level, the abnormalities that are induced may involve a wide variety of processes, but as yet no single aberration common to many viral infections has been found. The energy requirements of virus-infected cells appear to be closely similar to those of normal cells. Many metabolic alterations, however, have been found in virus-infected tissue; these include the appearance of new products, increased amounts of normal products and marked differences in the content of certain enzymes. As has been emphasized,<sup>14</sup> however, the precursor materials of low molecular weight that are utilized for the production of the macromolecules, nucleic acids and proteins, which have virus-specific properties, may be identical to those that are normally produced by the cell. If this be so, then apparently the major virus-specific abnormalities in biochemical activity are those leading to the formation of the necessary polymers and their assembly into virus particles. But, as was recently pointed out, "until the biochemical behaviour of the infected animal cell, the unit of viral disease, is clarified, it does not appear fruitful to consider in detail the problem of the biochemical pathogenesis of viral diseases in an intact multicellular organism".<sup>13</sup>

Whatever the nature of the more significant biochemical alterations may be, it seems evident that they may have large effects on the infected cell. In numerous instances they may be sufficiently critical to lead to marked deterioration and even to death of the diseased cell, as with animal cells infected with cytopathic human viruses or bacteria with virulent phages. In other instances, the alterations may affect less crucial processes and merely induce temporary damage from which the cell seems to recover, as in the case of chicken embryo cells infected with influenza or mumps virus, as well as in the spinal cord of the monkey infected with poliovirus.<sup>8</sup> In the special case of tumour-inducing viruses, of which so many have been discovered in animals during recent years, an enduring but often nonlethal aberration seems to be produced which may lead to continuing abnormal growth.<sup>15</sup>

If the biochemical alterations that arise in infected cells represent processes that are associated with viral reproduction, then it seems likely that they might continue as long as the reproductive process were fully active. If, however, there were to occur with increasing time a change in the quantitative or qualitative features of reproduction, some effect on the associated biochemical alterations might be anticipated. Striking changes in the process of viral reproduction as the duration of infection increases have been found to occur with a number of animal viruses. These appear to depend on changes in the micro-environment of the infected host cell and can be observed with

cultured cells *in vitro* as well as in the intact host organism. They can have marked effects on the extent to which the reproductive process proceeds, the number of virus particles that are produced and, most importantly, perhaps, on the properties of the new particles.

Relatively minor alterations in the environment of the infected cell—for example, small changes in temperature or pH—can produce large reductions in the number of new particles and also may lead to the production of attenuated or avirulent particles. This is especially evident with poliovirus and has made possible the selection of avirulent clones on multiplication at unusual temperatures.<sup>16</sup> At a temperature of 40° C., the extent to which poliovirus and several other agents multiply is considerably less than 1% of their multiplication at 37° C. A small increase in acidity has an equally striking effect, and at a pH of 6.7 the yield of new virus particles may be decreased by a factor of 500 or more.<sup>16</sup> When both temperature and acidity are increased, their effects are additive and the inhibition may be sufficient almost to stop viral reproduction. One of the most convincing demonstrations of the critical effect of temperature was made nearly 25 years ago when it was shown that certain plants can be cured of viral infection by growing them at 36° C.<sup>17</sup>

An even more remarkable effect is the induction of abortive reproduction through alteration of the micro-environment of the cell. Abortive reproduction leads to the production of noninfective virus particles which are not capable of initiating viral reproduction in susceptible host cells. With certain human and animal viruses it has been shown that abortive reproduction occurs when the number of virus particles in or on the cell is greater than about 10. As the number of particles increases, the number that are infective decreases, and eventually the yield becomes predominantly noninfective and therefore incapable of continuing the infective process.<sup>18</sup>

The capacity of the infected cell to produce new virus particles is surprisingly large; many single animal cells may produce as many as 1000 virus particles; in some instances, 10,000 or even 20,000. Because of this, the infected cell fairly promptly yields products which themselves alter the process of continuing viral reproduction. It needs to be emphasized that both infective and noninfective particles in sufficient number seem to have similar inhibitory effects, and either type of particle may induce abortive reproduction. Thus it appears that the reproduction of certain animal viruses may lead to self-inhibition. This situation is comparable to a feed-back mechanism which results in the production of fewer and fewer mature infective particles as more and more immature or non-infective particles are assembled. If this reaches the point that, on the average, less than one infective particle is produced per cell, it seems obvious that the infectious process cannot maintain

itself and must diminish in extent. Under these circumstances, certain viral infections appear, as it were, to drown in their own juice.

How frequently the phenomenon of abortive reproduction can be invoked as a factor contributing to recovery from viral disease is not yet clear. Certain viral infections that have been shown to induce abortive reproduction are indicated in Table V. To demonstrate that the phenomenon occurs requires that procedures be available for precise estimation of the number of both infective and noninfective particles that are produced. Such procedures have been developed for various hemagglutinating viruses, particularly those of the myxovirus group, but are not yet applicable to many other viruses.<sup>19</sup> That, on the reproduction of human and animal viruses, a large proportion of the new particles produced is not infective seems now to be well established. Excepting only vaccinia virus, other agents that have been adequately investigated appear to yield particles with an infective to non-infective ratio ranging from about 1:10 to 1:1000 or even more.<sup>20</sup> This suggests that abortive reproduction may be very common, but the available evidence does not yet warrant generalizations on the mechanisms that may induce it.

TABLE V.—VIRAL INFECTIONS THAT MAY LEAD TO ABORTIVE REPRODUCTION

Virus	Host
Influenza A.....	Chicken embryo, mouse, cultured cells
Influenza B.....	Chicken embryo
Swine influenza.....	" "
Mumps.....	" "

Abortive reproduction indicates production of noninfective virus particles.

The most recently discovered factors that may contribute to recovery are virus inhibitory substances that appear to be produced by the affected cells themselves. These substances, of which there may be several, seem to be proteins and are not related to the viruses that induce their production. One designated interferon<sup>21</sup> was found after cells had been exposed to inactivated influenza virus. Another, found in fluids from infected tissue cultures,<sup>22</sup> develops during the multiplication of poliovirus. These substances inhibit the reproduction of a number of different viruses, including poliovirus, measles virus, vaccinia and several myxoviruses. In addition, they inhibit the spread of virus particles from cell to cell. Should the production of these currently mysterious inhibitory substances be found to occur commonly during viral diseases, it seems evident that it would be necessary to consider them as factors which might favour recovery. Like abortive reproduction, they may represent previously unsuspected potentialities of the virus-infected cell which serve to limit viral multiplication and restrict extension of the infectious process within tissues.

Another factor which may be contributory is the exhaustion or elimination of susceptible cells. Once cells are infected with a particular virus they promptly become resistant to reinfection with the same agent. It is not necessary that they be damaged to become resistant, merely that they be infected in the sense that they are actively supporting viral multiplication. As more and more of the susceptible cells become infected, it is evident that fewer and fewer will remain in a state capable of supporting a continuing infection. Whether infected cells undergo deterioration leading to their death and physical elimination or are so little affected by the presence of the multiplying virus as to appear normal is not of importance in this regard. In either circumstance they become incapable of serving as hosts for the new virus particles that have been produced.

One of several possibilities may then occur. With virulent viruses which commonly lead to severe damage and cell death, most or all of the infected cells may actually be eliminated. This has been demonstrated to occur both in the upper respiratory tract of the living animal as well as in various cultured cells *in vitro*.<sup>1,4</sup> Since, in effect, susceptible cells are no longer present, the infectious process comes to a halt, and, if the damage has not been sufficiently extensive so as to lead to the death or enduring dysfunction of the host organism, recovery may occur.

Cells of a single type, whether in a living tissue or in culture, appear not to be uniformly susceptible to viral infection. Commonly a considerable number of resistant cells are present, possibly as a result of earlier mutations, and these not only fail to support viral reproduction but also provide a source of new cells which may permit regeneration to occur. As a consequence, even the most virulent and destructive viral infections generally do not eliminate all cells of a given type which might make recovery an unlikely possibility.<sup>23</sup>

With less virulent viruses which may alter but do not usually destroy cells, resistance to reinfection still develops in the cells which are infected. If infected cells continue to produce new virus particles throughout their lives but remain capable of dividing, the daughter cells produced can be expected to be infected also. Recently this has been demonstrated with certain animal cells in culture<sup>24</sup> and also has been found to occur with cells infected by certain tumour-inducing viruses.<sup>15</sup> If the rate of cell death balances the rate of production of cells through division, a steady state may develop in which the number of infected cells remains nearly constant.

This may be the situation with several plant viruses which tend to lead to chronic continuing infections that may show few signs but continue to be associated with the presence of infective virus. In view of the earlier comments on the possible contributions of abortive reproduction and inhibitory proteins to recovery, it should be pointed

out that chronically infected plants commonly contain infective virus in a concentration much below that present during the acute infection.<sup>6</sup>

If infected cells are unable to divide, as seems often to be the case, they will not produce infected daughter cells. New cells will then arise from uninfected cells which may be either resistant or susceptible but not yet infected. Such a process would be expected to favour the progressive selection of resistant cells which should eventually become predominant. Lacking an adequate supply of susceptible cells in which to continue multiplication, the virus will be less able to reproduce itself and so should eventually disappear. Under these circumstances recovery may be expected to be forwarded unless the resistant cells differ in other significant ways from those that were susceptible.

The emphasis that has been placed on occurrences at the cell level stems from the now widely accepted concept that the virus-infected cell is the biological unit of primary importance in these processes. This entity has properties that are different from those of either of the two components which are needed to form it. Most striking is its capacity to produce new virus particles, a feat that neither the virus nor the cell can accomplish alone. In contributing to this production, the cell is not unaffected and its physiology may be considerably altered.

Disease does not develop merely because cells are infected with viruses. In many instances, perhaps in most, viral infection is inapparent and gives no sign of its presence. However, when a sufficient number of cells are damaged and especially if they have highly important functions, as in the anterior horn of the spinal cord, then the signs and symptoms that are designated disease become apparent. It seems probable that recovery from disease, the return of adequate physiological function, is dependent on changes at the level of the virus-infected cell. That several separate mechanisms may be invoked to account for such changes seems apparent. It appears doubtful that any one of the contributing factors that have been discussed provides an adequate and generally applicable explanation for the recovery phenomenon. Taken together, however, they constitute a series of hypotheses which, if reasonable, can be used as guides for further study.

#### SUMMARY

Recovery is not only the most common issue of human viral diseases, it is for many the rule. In the great bulk of instances, episodes of human illness induced by viruses end in spontaneous recovery and only rarely lead to enduring abnormalities of physiological function.

An evaluation is presented of the several factors that are available to man which may contribute to the recovery process. It appears clear that it would not be consistent with well-established facts to contend that,

as a general principle, specific antibodies against viruses are important contributors to the recovery process.

Both the quantitative and qualitative features of viral reproduction may be affected by relatively minor alterations in the infected cell or its environment. Such alterations, which can result from the infection itself, may markedly inhibit reproduction and lead to the production of avirulent or even noninfective viral particles which are not capable of maintaining the infective process. This is comparable to the familiar feed-back mechanism in which the products of a reaction lead to its cessation.

Some recently discovered factors that may contribute to recovery are virus inhibitory substances—of which one has been designated interferon—that appear to be produced by the affected cells themselves.

Other factors which may be contributory are the exhaustion of the supply or the elimination of susceptible cells and the persistence of resistant cells which provide a source of new cells during regeneration.

It seems probable that recovery from viral diseases is dependent on changes at the level of the virus-infected cell and that several separate mechanisms can be invoked to account for such changes. It appears doubtful that any one of the contributing factors that have been assessed provides by itself an adequate and generally applicable explanation for recovery.

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## AUTOIMMUNIZATION — A POSSIBLE MECHANISM OF TISSUE INJURY\* II—CLINICAL ASPECTS OF AUTOIMMUNITY†

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THE TERM "autoimmune" is applied to certain diseases in which the plasma of patients contains antibodies against constituents of their own bodies.<sup>52</sup> Gear<sup>60</sup> suggested the term "autoallergic" since the group of diseases caused by exogenous antigens is generally referred to as allergic. MacKay *et al.*<sup>106</sup> narrowed the definition when they suggested the term "autoclastic" (self-destroying) for a group of pathologic entities in which the interaction of an autoantibody with its respective autoantigen is considered to have produced tissue injury. A similar meaning was conveyed by the term "diseases of autoaggression".<sup>36</sup>

Witebsky<sup>183</sup> has produced a series of postulates which he considered needed to be fulfilled before the connection between pathologic change and autoimmunization could be proved:

(1) It should be possible to demonstrate circulating or cell-bound antibodies; (2) the antigen involved should be characterized or even isolated; (3) antibodies should be produced against the same antigens in experimental animals, and (4) pathologic changes should appear in the corresponding tissue of an actively sensitized animal similar or identical to those seen in the human disease.

In recent years autoimmunity has assumed the status of a popular fad in clinical medicine. Autoimmune mechanisms have been imputed to be causative of many diseases of unknown etiology. Complete and conclusive proof is not yet forthcoming even in the most suggestive examples of "autoimmune diseases" using Witebsky's postulates<sup>183</sup> as a guide. Nevertheless abundant evidence has accumulated that autoimmunization may play a role in the causation of some conditions which will be discussed in further detail.

In view of the frequent finding of autoantibodies in a wide range of disease states, the clinician is faced with having to assign to them a possible role in the pathogenesis by a process of exclusion. An autoclastic mechanism will be acceptable to the clinician if all other causative factors can be ruled out. For example, the finding of anti-heart antibodies in myocardial infarction<sup>62</sup> obviously is unrelated to its causation, since the pathogenesis in this condition is so well defined. It has however

been suggested that the post-myocardial infarction syndrome may be due to an autoimmune reaction.<sup>48</sup> The clinician has come to realize that there are two types of circulating autoantibodies, i.e. one which merely represents a reaction to tissue injury and another which may be related to its causation.

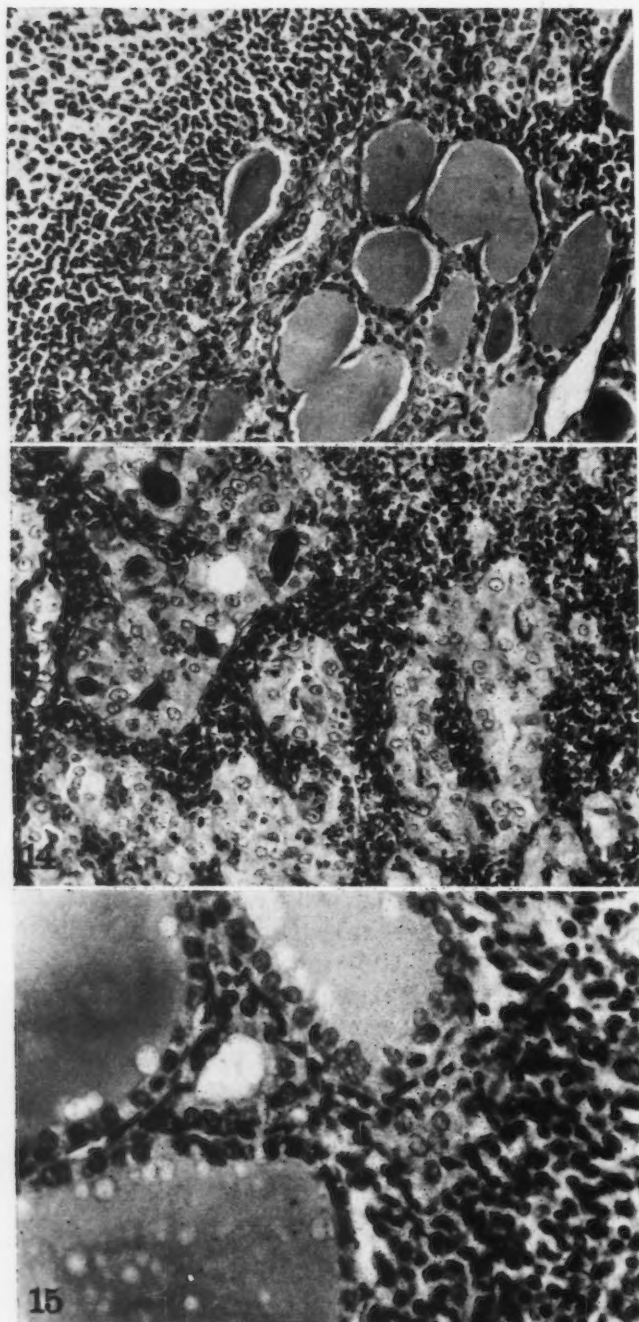
For purposes of clarity the diseases to be discussed will be dealt with under the headings of: (a) endocrine disturbances, (b) collagen diseases, (c) hematological disorders, (d) renal diseases, (e) neurological conditions and (f) liver diseases. It is not intended to review comprehensively all the entities which have at one time or another been thought of as autoimmune disorders. Rather will the analysis concern itself with broad principles and their possible application.

### (a) ENDOCRINE DISTURBANCES

In 1953 Fromm *et al.*<sup>57</sup> first demonstrated an elevated gamma globulin level in patients with Hashimoto's struma. Shortly thereafter Luxton and Cooke<sup>100</sup> found abnormal serum flocculation reactions in patients with the same condition. Subsequently Witebsky *et al.*<sup>181</sup> were able to demonstrate antithyroglobulin antibodies in patients with chronic thyroiditis by means of the tanned red cell hemagglutination technique (TRCA).<sup>12</sup> Almost simultaneously, Roitt *et al.*<sup>140, 141</sup> found similar antibodies in Hashimoto's disease using a precipitin test. This evidence, together with observations of experimentally induced autoimmune thyroid lesions,<sup>180</sup> led several investigators<sup>45, 126, 182</sup> to an initial hypothesis regarding the pathogenesis of Hashimoto's disease: leakage of thyroglobulin from thyroid follicles was thought to have evoked auto-antibody production, which then reacted with the colloid of intact thyroid follicles, produced further injury and leakage and more antibody formation. Thus a self-perpetuating destructive lesion was considered to have been established. The finding of these antibodies in many patients with idiopathic myxedema seemed consonant with this view.<sup>127, 143</sup> In addition Hashimoto's struma with high antibody titres has been found in association with other suspected autoimmune diseases such as systemic lupus erythematosus,<sup>107, 169</sup> rheumatoid arthritis,<sup>15</sup> idiopathic Addison's disease<sup>4</sup> and hepatic cirrhosis.<sup>100</sup>

The finding of myxedema with antithyroglobulin antibodies following mumps<sup>47, 54</sup> suggested a possible initiating factor, i.e. viral injury to thyroid cells with release of thyroglobulin from the follicles. Destruction of the follicular basement membrane was considered to be a possible cause of thyroglobulin release.<sup>152, 161</sup> Colloid spillage was demonstrated by the fluorescent antibody technique.<sup>178</sup> It still remained to be explained how antibody production could be perpetuated once the initial insult to the thyroid had subsided. This stumbling block seemed to be resolved with the demonstration of complement-fixing antibodies directed against cytoplasmic components of thyroid cells (micro-

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Parts of the investigations referred to in this review were supported by grants-in-aid from the National Research Council of Canada (MA-785 and MA-859).  
†This is the second of three instalments in which this article will be published. The complete bibliography will follow the final instalment.



Figs. 13 to 15.—These show proliferation of immunologically competent cells in the thyroid glands of three patients who all had high titres of circulating thyroid autoantibodies. Only in one of these (Fig. 14, Hashimoto's struma) are such cells thought to play a role in the pathogenesis of the disease. Neither primary idiopathic myxedema (Fig. 13) nor hyperthyroidism (Fig. 15) are thought to be caused by the proliferating immunologically competent cells, although in myxedema their participation has not been entirely ruled out. H. and E., Fig. 13,  $\times 304$ ; Fig. 14,  $\times 304$ ; Fig. 15,  $\times 637$ .

somal fractions).<sup>7, 143</sup> These were distinct from antithyroglobulin antibodies but were found in the sera of patients with Hashimoto's disease either alone or in combination with the TRCA antibody. Occasionally the latter type of antibody was found as an isolated phenomenon. In addition, the sera of some patients with Hashimoto's disease were found to contain antinuclear antibodies as well.<sup>76</sup>

It soon became apparent that these antibodies could be demonstrated in a wide variety of thyroid diseases, e.g. hyperthyroidism, non-toxic goitre, thyroid carcinoma, goitrous cretinism and occasionally in euthyroid normal persons.<sup>11, 27, 67, 143, 160</sup> In none of these is tissue destruction a paramount

feature. Furthermore, after therapeutic use of  $I^{131}$ <sup>27</sup> and during the course of subacute thyroiditis,<sup>47</sup> these antibodies were frequently demonstrable, often only to subside later without a self-perpetuating thyroid destruction. There is in fact no correlation between the titre of antithyroglobulin antibodies and the development of post- $I^{131}$  myxedema or temporary hypothyroidism in the course of subacute thyroiditis.<sup>160</sup> These observations throw doubt on the theory of thyroglobulin leakage as an invariable initiating cause of antithyroid autoantibody production. Further, tissue injury, despite the development of such antibodies, does not necessarily culminate in the development of Hashimoto's struma.

From the clinical point of view, therefore, the pathogenetic significance of the *circulating* autoantibodies against thyroid cells and thyroglobulin is not yet fully elucidated. It is probable that they are not actually cytotoxic agents but are a reflection of a variety of pathologic processes in the thyroid gland just as the proliferation of immunologically competent cells in the thyroid does not necessarily imply an autodestructive process (Figs. 13 to 15).

A number of other endocrine diseases, currently of unknown etiology, have some features suggestive of the participation of autoimmunization in their pathogenesis.

In *idiopathic Addison's disease* anti-adrenal antibodies have been demonstrated by Anderson and his colleagues<sup>4</sup> in two cases. Experimental autoimmune adrenal lesions have been produced with a pathologic appearance resembling its human counterpart<sup>156</sup> (Figs. 16 to 18).

The localization of a lesion in the *testis* (mumps orchitis) several days after mumps parotitis and its ready control with corticosteroid therapy might suggest an immunologic mechanism. Autoantibodies have not as yet been found in this condition though the experimental model of autoimmune testicular injury has been reported.<sup>56</sup> In some male patients with non-endocrine infertility antispermatozoal autoantibodies have been demonstrated.<sup>145</sup> These were also found in cases of idiopathic granulomatous orchitis and epididymitis.<sup>32</sup> In experimental animals depression of production of spermatozoa was noted in the presence of testicular lesions inadequate in magnitude to account for this phenomenon.<sup>175</sup> This suggests that a factor other than simple parenchymal destruction is concerned in the suppression of spermatogenesis; thus autoimmune depression of spermatogenesis may possibly occur in the human with no morphologic evidence of a specific autodestructive process of testicular tissue.

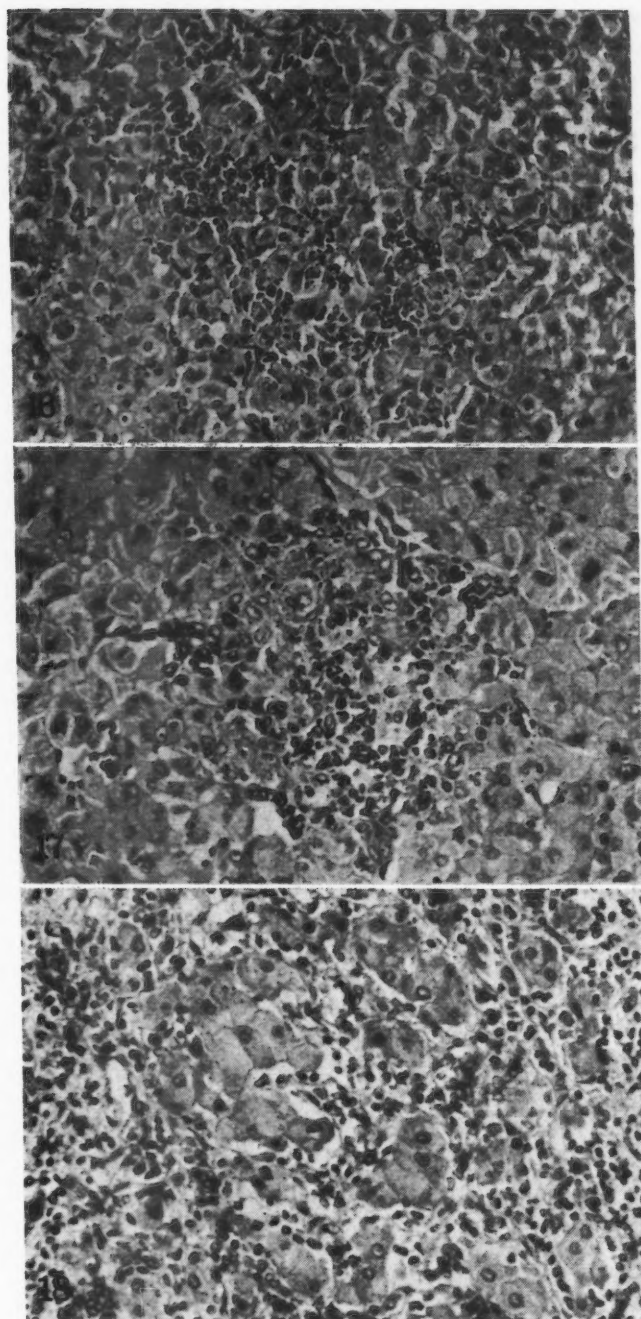
Speculation about *other idiopathic endocrine diseases* is unwise at this stage because of lack of evidence. The entities in which such evidence might be sought include: diabetes mellitus, hypoparathyroidism and possibly some types of hypopituitarism.

### (b) COLLAGEN DISEASES

Evidence has been accumulating that autoimmunization may play a role in the genesis of the so-called collagen diseases. This has been most convincing in systemic lupus erythematosus (SLE) and in rheumatoid arthritis.

Dameshek<sup>34</sup> considers *systemic lupus erythematosus* to be an example of an "autoimmune disorder par excellence". Clinically it may be characterized by an acquired hemolytic anemia, and hemolysins are often demonstrable.<sup>72, 94</sup> Thrombocytopenia and leukopenia are frequently present and are considered to be due to circulating antibodies.<sup>58</sup> A circulating gamma globulin which interferes with clotting has been found,<sup>77</sup> although its antibody nature has been doubted.<sup>133</sup> Although serositis and the clinical effects of vasculitis are major manifestations of systemic lupus erythematosus, no antibodies have yet been demonstrated against these tissues, nor indeed against clotting factors whose activity is often deranged. The involvement of the heart, kidney and liver in SLE is often accompanied by demonstrable autoantibodies<sup>59</sup> directed against these tissues. Antithyroid<sup>166, 169</sup> and anti-gammaglobulin<sup>85</sup> autoantibodies also have been demonstrated. On a cytoplasmic level, autoantibodies were found against isolated mitochondria and soluble cellular proteins,<sup>5</sup> as well as against microsomes.<sup>41</sup> Corticosteroids, which have a beneficial clinical effect, also appear to reduce the titres of these antibodies, and these rise again after cessation of this medication.<sup>172</sup>

Apart from the circulating anticellular and anti-tissue antibodies already mentioned, many other abnormal serological reactions occur in SLE. These include hypergammaglobulinemia, false positive Wassermann tests, positive Coombs' tests, cold agglutinins, cephalin-cholesterol flocculation tests, etc.<sup>28, 72, 94</sup> The most extensively studied is the so-called LE factor, a fraction of the gamma globulin not present in normal sera.<sup>73</sup> This factor reacts with nucleoprotein<sup>39</sup> and is responsible for the nuclear alterations resulting in the *in vitro* demonstration of LE cells. The LE factor is distinct from the antitissue antibodies.<sup>31</sup> Hematoxylin bodies, the *in vivo* counterpart of the LE phenomenon, are thought to be the result of a similar mechanism. Deicher *et al.*<sup>39, 40</sup> have studied the reaction between purified DNA and lupus sera. Positive precipitin and complement fixation reactions occurred in most instances irrespective of the source of DNA. It has been shown that the gamma globulin of lupus patients may be absorbed by nuclei of tissue cells from various human organs.<sup>76, 113</sup> Thus not only leukocytes but any parenchymal cells may be potentially destroyed by lupus antibodies. There is, however, no real proof that the LE factor is etiologically important.<sup>28</sup> It often appears only late in the disease, and there is no good correlation between its presence or titre and the clinical manifestations of SLE.<sup>72</sup>



Figs. 16 to 18.—These illustrate the similarity of experimental isoimmune and autoimmune and suspected autoimmune human adrenal lesions.

Fig. 16.—Proliferation of immunologically competent cells in adrenal cortex of guinea pig after injection of pooled guinea pig adrenal tissue in adjuvant. H. and E.,  $\times 243$ .

Fig. 17.—A similar lesion induced in a unilaterally adrenalectomized guinea pig by injections of its own adrenal tissue in adjuvant. Note the replacement of the parenchyma by the proliferating cells. Some investigators interpret this lesion as representing necrosis of parenchymal cells due to auto-digestion by histiocytes in the infiltrate. H. and E.,  $\times 225$ .

Fig. 18.—The adrenal gland of human case of idiopathic Addison's disease (cytotoxic adrenal contraction). Note the similarity to the appearance of the experimental prototypes. H. and E.,  $\times 377$ .

The complex lesions associated with SLE have not been reproduced experimentally though the vasculitis and glomerulonephritis in this disease bear many of the features of experimental hypersensitivity reactions.<sup>137</sup>

The initiation of this disorder by exogenous factors has not been excluded. The finding of a similar clinical and pathologic picture in patients<sup>134</sup> and animals<sup>30</sup> given hydralazine is suggestive of

this possibility. The alternate view, that genetic mechanisms may be involved in the production of this disease, is discussed below.

The evidence in favour of autoimmunization being involved in the causation of *rheumatoid arthritis* is similarly strong. As early as 1931 Nicholls and Stainsby<sup>122</sup> found an agglutinin against streptococci in patients with rheumatoid arthritis and suggested that it might be the cause of the disease. It was soon found that this reaction was non-specific since other bacteria were similarly agglutinated by the patient's sera. It was found subsequently that a macroglobulin constituent of the gamma globulin fraction of these sera reacted with the globulin coating of the bacteria or of red cells similarly enveloped but not with the actual cells themselves. This antibody, the rheumatoid factor,<sup>168, 185</sup> is found in most patients with rheumatoid arthritis and in approximately 16% of asymptomatic relatives of such patients.<sup>186</sup> The rheumatoid factor is actually an anti-antibody, the antigen being a "slightly shop-soiled" gamma globulin.<sup>52, 91</sup> The capacity of autologous gamma globulin to evoke an antibody response has been recently demonstrated experimentally.<sup>116</sup>

It has been suggested that this autoantibody is implicated in the production of the lesions in joints and connective tissue nodules. Mellors *et al.*<sup>114</sup> have shown that plasma cells in affected joints contain the antibody, and Taylor and Shepherd<sup>164</sup> that it is present in the fibrinoid deposits of rheumatoid nodules. However, in both the aforementioned

connective tissue diseases passive transfer of the circulating antibody, either to normal volunteers<sup>28</sup> or transplacentally to the fetus,<sup>14</sup> fails to induce clinical manifestations of these diseases. The most tangible evidence that circulating autoantibodies are not implicated in the pathogenesis of rheumatoid arthritis lies in the high incidence of this disease in children with agammaglobulinemia.<sup>66</sup>

Burnet's clonal selection theory<sup>21</sup> suggested that these disease entities may be genetically conditioned anomalies of antibody production. Some support for this concept has been put forward by Ziff,<sup>187</sup> who draws attention to the following points: (1) overlapping of the symptoms and signs of the connective tissue diseases with each other as well as with agammaglobulinemia, Sjörger's syndrome, chronic thyroiditis and others; (2) the familial occurrence of rheumatoid arthritis, SLE and agammaglobulinemia; (3) the occurrence of connective tissue diseases in relatives of probands often differing from that of the proband, and (4) the presence of a number of abnormal gamma globulin factors in the sera of asymptomatic relatives in patients with connective tissue diseases. Thus, although evidence for a genetic predisposition is forthcoming, many questions are still unanswered: Why do some persons who have such circulating antibodies fail to develop any clinical disease? Why may the same fundamental genetic anomaly find expression in different disease entities in relatives? What is the mechanism by which the genetic anomaly is translated into a tissue injury?

(To be continued)

#### EFFECT OF AUTOLOGOUS BONE MARROW ON THE CYTOPENIAS INDUCED BY NITROGEN MUSTARD\*

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In 1949, JACOBSON *et al.*<sup>1</sup> demonstrated the protective effect of spleen shielding in mice exposed to doses of total body irradiation which were lethal to unshielded mice. Intravenous injection of homologous bone marrow in mice and guinea pigs protected the animals against lethal doses of irradiation.<sup>2</sup> The mechanism of this protection was shown to be attributable to repopulation of hematopoietic tissues by the infused marrow.<sup>3</sup> Weston

*et al.*<sup>4</sup> reported that in rats recovery from bone marrow aplasia produced by busulfan (Myleran) could be achieved by bone marrow infusions. Isologous but not homologous bone marrow gave some protection to mice which received lethal doses of nitrogen mustard.<sup>5</sup> Autologous nucleated marrow cells will protect dogs from doses of total body irradiation up to 1500 r, and the recovery of these animals is more certain than is that of dogs treated with homologous marrow.<sup>6, 7</sup>

While there are a variety of techniques which can be employed to demonstrate a "take" after the infusion of homologous marrow, these techniques cannot be used to judge the function of infused autologous marrow. The present investigation was planned to study the effects in patients of an infusion of fresh autologous bone marrow on the cytopenias which result from a single intravenous infusion of nitrogen mustard (methyl bis(B-chloroethylamine) hydrochloride) in a dose of 0.4 mg. per kg. of body weight.

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Presented at the 1961 Annual Meeting of the Royal College of Physicians and Surgeons of Canada, Ottawa, January 1961.  
†With the technical assistance of Margo Grace and Cecile Bélanger.

MATERIALS AND METHODS

Ten patients with malignant diseases which might be palliated by treatment with nitrogen mustard were selected for inclusion in the study. With the exception of one patient who had received nitrogen mustard four months previously, none of the group had had chemotherapy or radiotherapy in the previous year. No evidence of bone involvement by the malignant disease was present on clinical examination, in a radiological survey of the skull, chest, spine and pelvis, or in smears and sectioned particles of aspirated bone marrow. Patients with gastrointestinal lesions which might bleed, or with renal disease or infections, were excluded.

identification of 300 cells. The mean of two sets of pretreatment observations on each of the ten patients was recorded and the observations were repeated on day one, and at intervals of four days for a total period of 26 days.

Bone marrow was collected with aseptic technique from the posterior iliac crests, under local anesthesia, using a 14-gauge University of Illinois needle. As each 5 ml. of material was aspirated, the needle was advanced into the marrow cavity, or withdrawn and reinserted in a new site. Syringes were lubricated with tissue culture fluid (M-150)\* containing 20 units of heparin per ml. The aspirate was transferred through a large bore needle, which contained in its hub a fine wire mesh, to a vacuum

TABLE I.—CLINICAL FEATURES OF TWO GROUPS OF PATIENTS

GROUP I.—NITROGEN MUSTARD ONLY				GROUP II.—NITROGEN MUSTARD PLUS BONE MARROW			
Patient	Diagnosis	Age	Sex	Patient	Diagnosis	Age	Sex
1	Malignant melanoma . . . . .	84	♀	6	Reticulum cell sarcoma . . . . .	64	♂
2	Hodgkin's disease . . . . .	74	♀	7	Carcinoma of prostate . . . . .	78	♂
3	Adenocarcinoma of colon . . . . .	50	♀	8	Carcinoma of lung . . . . .	62	♂
4	Hodgkin's disease . . . . .	77	♂	9	Carcinoma of sigmoid colon . . . . .	60	♀
5	Fibrosarcoma of leg . . . . .	69	♂	10	Carcinoma of uterine body . . . . .	65	♀
Mean		70		Mean		66	

Five of the patients received methyl bis(B-chloroethylamine) hydrochloride (HN<sub>2</sub>), 0.4 mg. per kg. of body weight, in a single intravenous injection. The remaining five patients received the same dose of nitrogen mustard (HN<sub>2</sub>) but, two hours later, were given fresh autologous bone marrow removed immediately before the administration of the nitrogen mustard.

The clinical features of the two groups of patients are shown in Table I and the pretreatment hematological findings in Table II.

bottle† containing heparinized M-150 maintained at 4° C. Approximately 100 ml. of aspirate was mixed with an equal volume of heparinized tissue culture fluid. The mixture was centrifuged at 600G for 15 minutes in a refrigerated centrifuge at 4° C. and any visible supernatant fat was removed by suction. The cells were resuspended by gentle mixing and maintained at 4° C. until their re-administration to the patients, without filtration, within two to three hours of their removal and approximately two hours after the injection of nitrogen mustard. The total number of nucleated cells reinfused varied from 1.3 to 3 x 10<sup>9</sup>. There

TABLE II.—PRETREATMENT HEMATOLOGIC FINDINGS IN TWO GROUPS OF PATIENTS

GROUP I.—NITROGEN MUSTARD ONLY					
Patient	Packed red cell vol. %	White cell count No./c.mm.	Granulocytes No./c.mm.	Lymphocytes No./c.mm.	Platelets No. × 10 <sup>9</sup> /c.mm.
1	37	7000	6160	840	260
2	35	6100	5429	671	237
3	33	9800	7546	2254	250
4	37	5160	5160	840	220
5	42	9500	7740	1760	212
Mean	37	7500	6300	1200	235

GROUP II.—NITROGEN MUSTARD PLUS BONE MARROW					
Patient	Packed red cell vol. %	White cell count No./c.mm.	Granulocytes No./c.mm.	Lymphocytes No./c.mm.	Platelets No. × 10 <sup>9</sup> /c.mm.
6	34	9100	4828	3822	238
7	34	13,000	8580	4420	280
8	41	6700	5427	1273	240
9	40	5200	3900	1300	200
10	39	9500	8360	1140	340
Mean	37	8700	6100	2300	259

All hematological determinations were carried out by one experienced technician (M.G.). Red and white cell counts and packed cell volumes were determined by standard techniques.<sup>8</sup> National Bureau of Standards pipettes and chambers were used for counts. Platelet counts were done by phase microscopy.<sup>9</sup> Differential counts were based on the

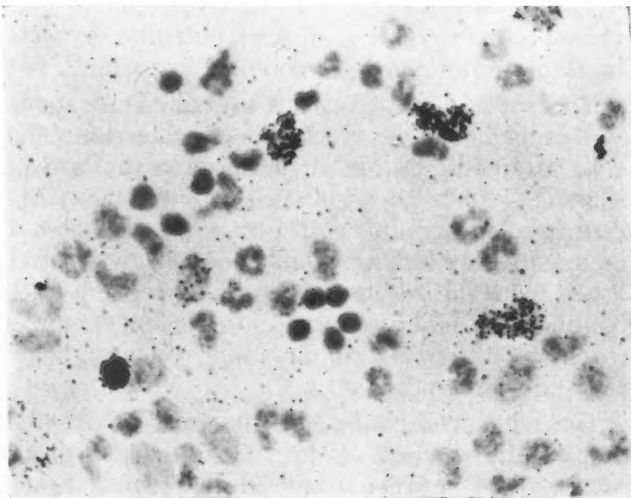


Fig. 1.—Photomicrograph of autoradiographic preparation of bone marrow aspirate.

\*M-150 is modified TC 199 with pH of 7.2, kindly supplied by Dr. Joseph Morgan, Chief of the Biochemistry Division, Laboratory of Hygiene, Ottawa.  
†Supplied through the courtesy of Mr. Charles Woods, Abbott Laboratories.

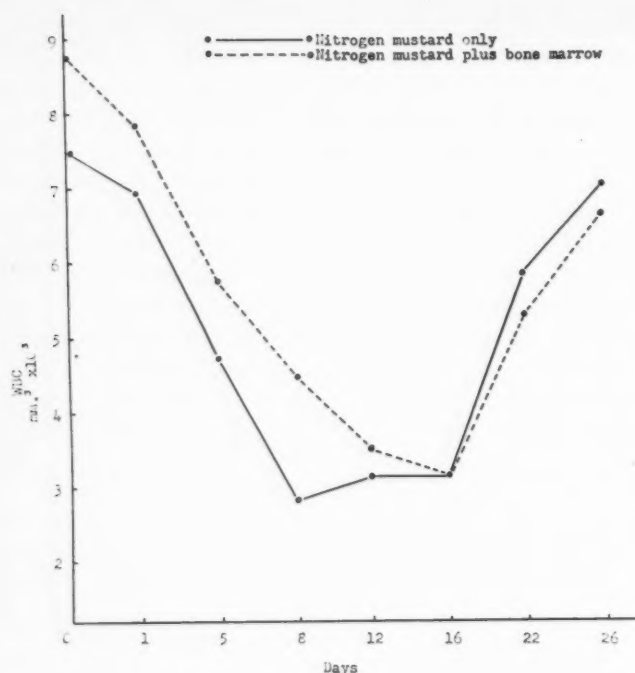


Fig. 2.—Total white blood cell count.

were no immediate or delayed ill effects from the infusions.

Marrow aspirates collected as described showed the various elements to be well preserved in stained smears. To ensure that viable cells capable of division were reinfused, aliquots of marrow collected and handled as described were maintained at 4° C. for three hours, and were then incubated for one hour at room temperature with tritiated thymidine. Autoradiographs<sup>10</sup> prepared from concentrates of the incubated marrow suspension showed many cells (usually about 10% of the nucleated cells) to be intensely labelled (Fig. 1).

### RESULTS

The mean values for the various peripheral blood elements in the two groups of patients, expressed in absolute numbers, are compared in Figs. 2 to 6.

The solid lines in Figs. 2 to 4 demonstrate the well-known changes which occur in the white blood cells after administration of nitrogen mustard.<sup>8</sup> A slight fall in total white cell count, owing to a decrease in lymphocytes, occurs in the first 24 hours; by the fifth day leukopenia is well established, with the addition of granulocytopenia to the lymphopenia. The depth of the leukopenia is reached on the eighth day and recovery begins after the sixteenth day.

The white cell changes in the "marrow treated" group parallel those of the "mustard only" group. At any point between 1 and 26 days after nitrogen mustard administration, the mean total white cell count, lymphocyte or granulocyte counts (Figs. 2 to 4) in the "marrow treated" group do not differ significantly (more than two standard deviations) from the mean of the "mustard only" group on that day.

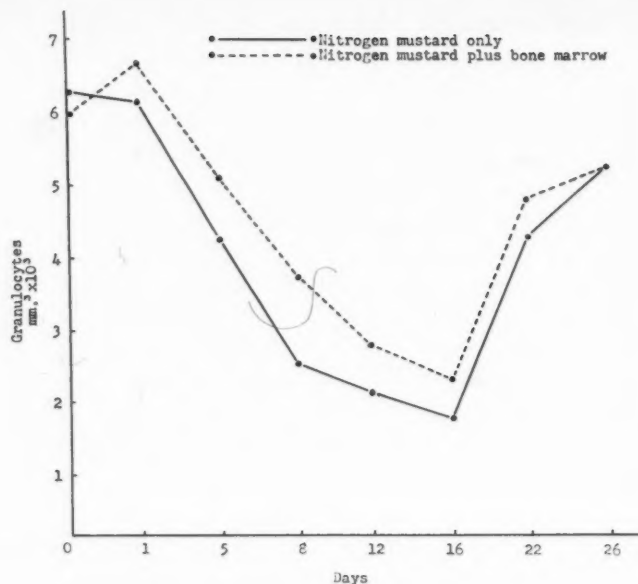


Fig. 3.—Absolute granulocyte counts.

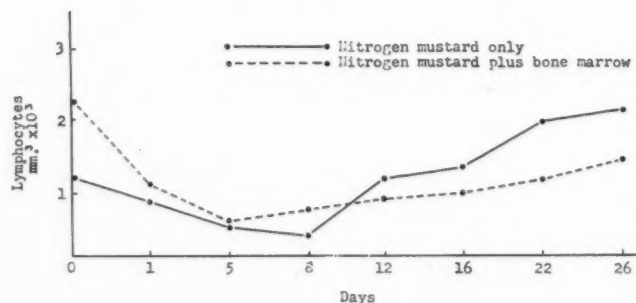


Fig. 4.—Absolute lymphocyte counts.

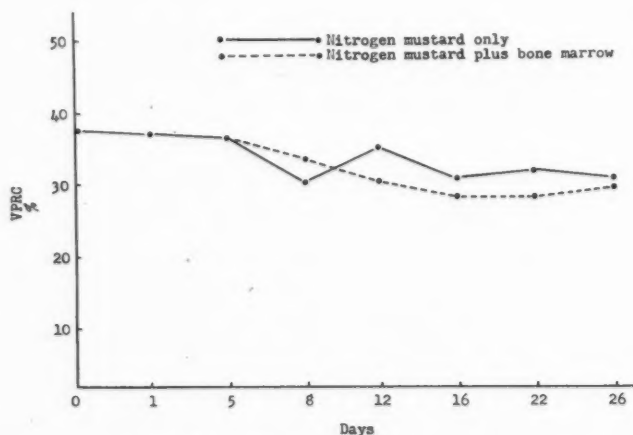


Fig. 5.—Volume of packed red cells.

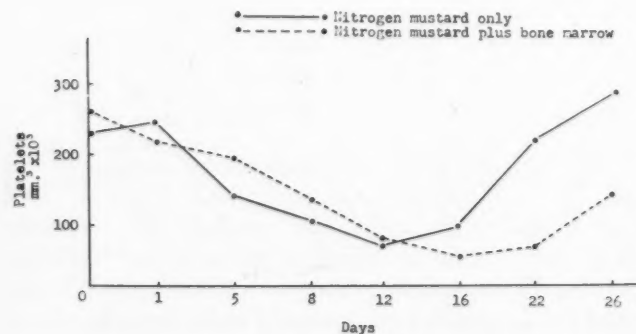


Fig. 6.—Platelet counts.

Figs. 5 and 6 demonstrate that changes in the volume of packed red cells and platelet counts also parallel each other closely in the two groups. Fig. 6 might suggest that recovery from nitrogen mustard-induced thrombocytopenia was less complete in the "treated" group, but the differences from the mean of the control group on these days are less than two standard deviations.

#### DISCUSSION

Under the conditions of the present study, no effect of infused autologous marrow was demonstrated on the depth or the duration of the various cytopenias which follow the administration of a single 0.4 mg. per kg. dose of methyl bis(B-chloroethylamine) hydrochloride. If cells capable of implantation and subsequent production of mature peripheral blood elements were infused in sufficient numbers, the mature elements might be expected to appear in the peripheral blood in increasing numbers from the second day after the infusion.<sup>11</sup> Failure to demonstrate differences between the control and marrow-infused groups of patients might be explained in three ways. Firstly, viable cellular elements capable of division might not have been reinfused. Our observations that marrow collected by the technique described contains cells capable of DNA synthesis makes this possibility unlikely. Secondly, the viable infused cells might be exposed to the action of the nitrogen mustard given two hours previously. Timing of the reinfusion of marrow after the nitrogen mustard was based on evidence that the cytotoxic action of methyl bis(B-chloroethylamine) hydrochloride has been dissipated within 10 minutes of its intravenous injection.<sup>12, 13</sup> Failure to detect an effect on the depth or the duration of the cytopenias may also be due to infusion of insufficient numbers of autologous cells with the capacity to produce peripheral blood elements in sufficient quantities to cause detectable differences between the two groups of patients. Spontaneous marrow recovery would mask any contribution from the infused cells.

The results of this study are difficult to reconcile with the reports of Newton *et al.*<sup>14</sup> on the effects of frozen autologous marrow (approximately  $1 \times 10^9$  nucleated cells) on the peripheral blood elements of patients who were leukopenic after irradiation. A rapid rise in the white cell count occurred immediately after the marrow infusion; this was postulated to be due to a "non-cellular humoral factor". From the published figures, the last white cell count, 14 days after the marrow infusion, was lower than the leukocyte count before the infusion (Case 1). In the second patient, the white cell count appeared to be unchanged after one week following the preinfusion counts, and was normal by three weeks. Marrow regeneration in these patients was said to occur, but this statement seems to be based on the results of serial total nucleated counts of marrow aspirates. The cellularity of mar-

row aspirates varies greatly with the degree of peripheral blood admixture, and total nucleated counts are of no value as an index of marrow cellularity.<sup>8</sup> Observations on the effect of nitrogen mustard plus autologous marrow have been published by Black, Speer and Stone.<sup>15</sup> Much smaller amounts of aspirate were used than in our study. While the authors concluded that recovery from the leukopenic effect of nitrogen mustard was more rapid when autologous marrow was simultaneously infused, the trials were not controlled by observations on comparable patients who had not received autologous marrow. McFarland, Granville and Dameshek<sup>16</sup> administered autologous marrow ( $2 \times 10^9$  nucleated cells) to five patients, four hours after the administration of nitrogen mustard in large doses (1.1 mg./kg.). The effect could not be judged, because no control cases were studied. Kurnick *et al.*<sup>17</sup> have reported the effect of the infusion of preserved marrow (400 million nucleated cells) on the pancytopenia which followed extensive radiation. Three of four patients showed recovery of their pretreatment blood counts in 10 to 40 days; the fourth patient died on the tenth day. On the basis of serial marrow particle sections, recovery of normal cellular marrow was demonstrated. Ten control patients were studied and showed incomplete or slow recovery of peripheral counts and marrow cellularity after six months or longer. In two groups of patients, such as we have studied, differences in the degree of the cytopenias might have emerged had the two groups of patients been much larger or if a more severe degree of hematopoietic depression had been induced by larger doses of nitrogen mustard. Experimental work on mice has shown a protective effect of isologous marrow on the survival of mice given an LD<sub>50</sub> dose of nitrogen mustard.<sup>5</sup> A controlled study in which potentially lethal doses of nitrogen mustard are used is not justifiable in human patients.

#### SUMMARY

The effect of intravenous infusions of fresh autologous bone marrow aspirates on the various cytopenias induced by methyl bis(B-chloroethylamine) hydrochloride has been studied. No difference in the depth or duration of the cytopenias could be demonstrated between a group of patients who received nitrogen mustard only and a group who received fresh autologous bone marrow after the nitrogen mustard.

The results have been interpreted and discussed.

Fresh bone marrow aspirates which contain  $1$  to  $3 \times 10^9$  nucleated cells were not found to alleviate the cytopenias which result from conventional doses of methyl bis(B-chloroethylamine) hydrochloride.

The authors wish to acknowledge the contribution of Mrs. Jacqueline Brown and other members of the medical nursing staff to this study. The investigation was supported by a grant-in-aid from the Ontario Cancer Treatment and Research Foundation. NTB<sub>2</sub> emulsion for autoradiography was supplied by Eastman Kodak Co. (Rochester, N.Y.).

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### DYSTROPHIA MYOTONICA IN ASSOCIATION WITH MENTAL DEFECT

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DYSTROPHIA MYOTONICA, myotonia atrophica, or Curschmann-Steinert disease, is numbered amongst the less common causes of mental defect. Typical cases, especially those with supporting pedigree, offer little difficulty in diagnosis, but uncertainty may arise in abortive forms. Characteristically the disease is distinguished by muscular atrophy of typical distribution, myotonia, and other dystrophic symptoms such as cataract, testicular atrophy and frontal baldness.

Muscular atrophy is usually most evident in facial muscles, masticatory muscles and sternomastoids. Facial involvement, with its orbicular weakness, partial ptosis, shrinkage of masseters and temporales, and atrophy of sternomastoids, gives rise to the typical hatchet-face and pole-neck appearance. Moreover, the face is expressionless, or at most gives an impression of slight sadness; the mouth frequently remains partially open from weakness of the muscles of mastication, and the voice is generally low, weak and nasal from weakness of laryngeal and pharyngeal muscles. At the same time the limbs show more or less symmetrical wasting and weakness of peripheral muscles with ultimate spread to proximal muscles. Wasting is generally slow in progression but is occasionally rapid with considerable involvement of affected musculature within a year. Eventually the process is fairly general. In some cases monosymptomatic or abortive types of the muscular complex occur. Fibrillation is not a feature of this form of atrophy.

Myotonia is usually present in hands, face and tongue, but although occasionally more extensive it lacks the widespread distribution characteristic of myotonia congenita. In the myotonic reaction, affected muscle fibres exhibit greatly increased sensitivity to mechanical stimulation, with resultant delay in muscular relaxation following sustained

forceful contraction, and slowness in executing movements. A characteristic electromyographic pattern has been described in which repetitive local discharge occurs asynchronously from individual muscle fibres and groups of fibres, high initial frequency declining rapidly and discharge ceasing within a few seconds. When the flexors of the fingers are involved, as is commonly the case, the patient has difficulty in relaxing his grasp. Similarly, strong closure of the eyes may be followed by long delay in relaxation. The presence of myotonia is also apparent in the response to percussion over affected muscles; tapping results in a prolonged contraction with persistence of visible dimpling or ridging for a few seconds. Myotonia is generally accentuated by cold, but with increasing atrophy of muscles it may diminish and disappear.

A number of other abnormalities are of frequent occurrence. Cataract is present in fully a third of cases and may appear in relatives who show no other evidence of dystrophy. It commences typically as punctate and linear multi-coloured opacities in the anterior and posterior subcapsular zones. Frontal baldness has often been described, as has testicular atrophy with subsequent impotence and sterility. Although pathological changes in the ovaries are apparently uncommon, Perkoff and Tyler<sup>15</sup> mention the fairly common occurrence of menstrual disturbances in affected females. Radiological changes are common and include thickened skull vault, hyperostosis frontalis interna, enlarged sinuses and small pituitary fossa. Cardiac abnormality affects about 50% of cases. Latent heart block and bundle branch block are the most common anomalies, but complete heart block and cardiac enlargement have been described. The myocardium is believed not to show changes of the type seen in skeletal muscle. However, Rinzler<sup>17</sup> draws attention to the gross myocardial lesions occurring in the allied disorder of Duchenne or childhood type of progressive muscular dystrophy. On the other hand, Waring, Ravin and Walker<sup>22</sup> consider that, despite frequent hypotension, the changes observed are such as to suggest coronary sclerosis. One of their cases showed definite evidence of myocardial infarction. Urinary creatine excretion may be increased in dystrophia myotonica as in other forms of wasting, whether due to

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muscle disease or denervation. Similarly, serum aldolase may be slightly raised, although it does not show the gross elevation described by Thomson, Leyburn and Walton<sup>19</sup> as typical of the Duchenne type of muscular dystrophy.

The mental state in dystrophia myotonica has received attention from a number of investigators. Maas<sup>10</sup> drew attention to lack of drive and initiative along with a tendency to unsociability or even sullenness, which appeared to be of frequent occurrence in sufferers from the disease. Stephens<sup>18</sup> regarded indolence and excessive self-satisfaction and self-esteem as common characteristics. Purves-Stewart<sup>16</sup> remarked on a curious abnormal cheerfulness occurring in many cases. Colombati, Reda and Frighi<sup>5</sup> described a Rorschach pattern of egocentricity, poor elasticity of thought and incapacity for affective adaptation, which, along with reduction of the critical faculty, they considered indicative of an element of frontal psychological syndrome, and hence representing a different mental picture from what they believed to be the ordinary oligophrenic background of myopathies in general. Gottwald<sup>7</sup> went so far as to suggest that psychopathological changes, notably lack of impulse, were nearly always present, and that it was not unknown for such changes to reach psychotic intensity. On the other hand, Waring, Ravin and Walker<sup>22</sup> concluded that changes in temperament were infrequent, and that in those cases in which they did occur they seemed more of a reaction to bodily defects than the result of any special congenital or degenerative mental change. Possibly the most comprehensive survey was that made by Klein<sup>9</sup> in Switzerland. A total of 319 cases of dystrophia myotonica were recorded in that country over the period 1945-1956. Of this number 244 were available as a basis on which to estimate psychic abnormality. In 86 cases (35.2%) psychic abnormality was considered to be present. Affective and character disorders were found in 32 cases (13.1%) whereas low intelligence was present in 54 cases (22.1%). The intellectual factor was likewise stressed by Brain,<sup>4</sup> who considered that in affected families there existed evidence of a decline in social status over several generations. Low intelligence in dystrophia myotonica may be due to either mental defect or dementia. There is no doubt that intellectual deterioration can occur during the course of the disease, and that consequently the mental state may be such as to constitute certifiable dementia. Nevertheless, there is some basis for the belief that mental defect may be at least as prevalent as dementia. Maas and Paterson,<sup>11</sup> for example, found amongst their 17 cases of dystrophia myotonica with low intelligence 6 cases where low intelligence was attributable to dementia, compared with 11 cases due to mental defect. When the onset of physical signs has occurred in childhood, mental defect of moron or imbecile grade has frequently been encountered. Mental defect can precede the onset of physical

signs and, as Aird<sup>2</sup> has pointed out, may be present from birth.

Dystrophia myotonica commonly manifests itself in the third decade. According to Penrose,<sup>14</sup> the mean age of onset is 24 years, with a standard deviation of 13 years. Still, onset even in early infancy is not unknown and Vanier<sup>21</sup> has described six such cases. Age of onset is apt to differ between parents and children but to remain constant for siblings. The disease is inherited as a dominant trait with varying manifestation. Fleischer<sup>6</sup> suggested that the disease was inherited latently for several generations and then became evident at an earlier age in families of the next generation. Commonly a grandparent with senile cataract and a parent with presenile cataract are followed by a generation showing muscular dystrophy, myotonia and other symptoms. In some cases no abnormality has been described in antecedents. Penrose<sup>13</sup> believes the severity of the clinical picture may depend less on the main gene for dystrophia myotonica than on the nature of the allelic gene which accompanies and modifies it. The concomitant transmission of muscular wasting, myotonia and cataract is an unusual combination, but possibly not unique. Wilson<sup>8</sup> quoted a pedigree originally reported by Hamilton in which peroneal muscular atrophy and cataract were inherited separately or in combination, and where the former author considered that some of the recorded phenomena suggested the presence of myotonia. Further uncertainty exists concerning the relationship of dystrophia myotonica to myotonia congenita and paramyotonia. Although Bell<sup>3</sup> considered these independent disorders, the occurrence of mixed syndromes and the description of pedigrees with both dystrophia myotonica and myotonia congenita led Nattrass<sup>12</sup> to consider all three disorders as part of a single disease process, and to suggest the generic term of "myotonic syndrome".

Demonstrable pathological changes in the muscles include initial increase in the number of sarcolemmal nuclei, swelling and fragmentation of muscle fibres, and ultimately considerable replacement of muscle by fat and fibrous tissue. According to Adams, Denny Brown and Pearson<sup>1</sup> the presence of long rows of sarcolemmal nuclei in otherwise intact muscle fibres is diagnostic of dystrophia myotonica. Various endocrinopathies have been reported from time to time involving pituitary, thyroid and suprarenal glands. A fairly constant finding on testicular biopsy is tubular degeneration. Atrophic changes in cortical neurones have been described by Trelles *et al.*,<sup>20</sup> and proposed tentatively as an organic basis for mental abnormality.

The following patient was admitted to the Manitoba School on February 18, 1957. The patient, a woman aged 33 years, the second eldest of six siblings, had been regarded by her relatives as intellectually retarded from birth. Her developmental history showed a delay in all spheres; thus

sitting up, for example, did not occur until 11 months, walking was delayed until 19 months, and speech did not appear before 36 months. Scholastically her record was poor, and although she remained at school for six years she appeared to have acquired little more than an elementary knowledge of reading. The age of onset of physical symptoms is harder to place, but clumsiness in using the hands was first observed during the earlier years at school. In adolescence a tendency to stumble became noticeable. After leaving school she remained at home until increasing unsteadiness and weakness of muscles created too great a problem for her ageing mother to cope with.

The change in her circumstances brought about by admission did not cause any undue upset and she settled down to a simple routine which demanded little more than the infrequent performance of light tasks about the ward. Anything requiring strength or persistence was manifestly beyond her capabilities. Apart from muscular weakness she was subject to profuse menses, and in 1959 a subtotal hysterectomy showed the uterus to be extremely distorted by intramural fibromyomas. No significant change was found in the ovaries.

On examination the patient presented the typical appearance of dystrophia myotonica. Her face was long and pointed with drooping eyelids, sagging lower jaw and partially open mouth. Her cheeks were hollowed from atrophy of the masseters, the orbicular and oral muscles were weak, and the effect generally was to create an expression of permanent glumness. A moderate recession of the hair line was present. Her speech was weak, indistinct and nasal in quality. The sternomastoids were partially reduced in strength and volume. Peripherally, generalized muscular feebleness was present. The forearm muscles were weak, the most marked involvement affecting the flexors and extensors of the fingers. The small hand muscles were less affected and the thenar and hypothenar eminences were moderately atrophic. Considerable wasting was apparent in the legs. The anterior tibial and peroneal muscles were especially affected; dorsiflexion of the foot was very weak and eversion was impossible. Wasting was more obvious in the left leg, where the foot was partially inverted. Foot drop was present on both sides. Quite marked wasting and weakness were present in both quadriceps, whose impaired action barely enabled the patient to raise her legs high enough to counteract the foot drop. Her gait was therefore hesitant and she stumbled frequently.

Voluntary myotonia was not always present, but occasionally could be demonstrated in the slow relaxation of grasp. On the other hand, mechanical myotonia could often be elicited from the thenar eminence, and when absent there, prolonged localized muscular contraction was generally apparent in the visible dimpling which followed percussion of the tongue.

In the nervous system, apart from slight diminution of tendon reflexes, no abnormality was detected, and an electroencephalogram was found to be within normal limits. Her vision was apparently unimpaired, and in each eye the cornea, anterior chamber and iris were normal. Slit lamp investigation of the lens was not performed. Her Wassermann reaction was negative; her basal metabolic rate was estimated to be +5, and her blood cholesterol level 226 mg.%. Her blood pressure was 110/72 mm. Hg and her pulse rate varied between 64 and 82 per minute. The electrocardiogram showed a PR interval of 0.24 second, consistent with latent heart block. In addition, flat T waves were found in lead I, in association with elevated S-T segments in leads II, III and VF. Radiographic examination of the skull showed hyperostosis frontalis interna and generalized thickening of the vault in the parietal and occipital regions.

On the Wechsler Adult Intelligence Scale, the patient obtained a verbal score of 53, a performance score of 58, and a full-scale I.Q. of 52. Her score on all 11 sub-tests was uniformly low. Emotionally she was flat, and although she occasionally complained about the other girls in the ward, there was little evidence of intensity or persistence of feeling. Otherwise her outstanding characteristics were self-satisfaction and indolence, but the latter was probably no more than might be expected, in view of her physical and mental state. The pattern which emerged from a series of Szondi tests indicated mainly profound egocentricity, poor adaptability and marked indifference to her environment.

Further evidence of dystrophia myotonica was obtained from the family history. Examination of this history, from which consanguinity was absent, showed that the patient's father had cataract and that in his generation two cousins had severe dystrophy. Moreover, of his eight siblings two had physical disability. Thus, a sister had been able to carry on at her profession of teaching until the age of 45, but increasing weakness in the legs and neck proved incapacitating, and after years of invalidism she died at the age of 55. A brother was known to be afflicted at the age of 21. He does not appear to have been capable of any responsible work, and until finally disabled by muscular weakness and failing vision was employed doing simple routine jobs on a farm. In the patient's own generation her five siblings showed no obvious signs of the disease, and all had satisfactory scholastic and socioeconomic records. A cousin, however, had been affected with weakness of the legs and mental defect. Impairment of gait was obvious by the age of about eight years, and at school he was able to acquire little more than the ability to write his name. At the age of 23 he was considered beyond parental control and was admitted to the Manitoba School. By this time his feet were quite crippled and it was recorded on admission that they tended to assume a position of mild talipes equinovarus.

Apart from weakness and wasting of the legs, he did not appear to have any further abnormality affecting the musculature or nervous system. His I.Q. on admission was 54 on the Terman-Merrill Scale. At the age of 29 he developed symptoms of myocardial weakness during the course of a bronchopneumonia and died suddenly. His two siblings had already predeceased him at the ages of four and five years respectively, each dying suddenly following what was described as a series of heart attacks.

#### COMMENTS

The association of dystrophia myotonica with mental defect is apparent in the present case. The second eldest of six siblings, she was the only mental defective and at the same time the only manifest case of dystrophy. However, a cousin with atypical dystrophy had also been mentally defective. In both cases mental retardation and physical symptoms of the disease were apparent in childhood. In the preceding generation the patient's father had had cataract but normal intelligence. An aunt of the patient who developed dystrophy later in life had been of normal intelligence. On the other hand, an uncle whose disease was established by the age of 21 years appears to have been of sub-normal intelligence. A cousin of the patient, later certified as a mental defective, had shown weakness of the legs by the age of eight years. The family history is thus in keeping with Penrose's<sup>14</sup> observation that mental defect is an accompanying symptom when dystrophia myotonica is of early onset. Indolence, regarded by some as a characteristic feature, was also present in the patient, although the impression existed that it could be attributed in large part to her general infirmity. On the other hand, the marked egocentricity and other aspects of her mental state demonstrable by projective techniques were strongly reminiscent of the pattern described by Colombati and his colleagues.

In the case of the cousin who had been certified mentally defective, the distribution of the pathological process had proved misleading. Here the disease appears to have been abortive and restricted to the legs. A distribution of this type is of

interest in the light of the pedigree quoted by Kinnier Wilson. A further unusual feature is the incidence of fatal cardiac involvement. This particular cousin died suddenly following development of myocardial weakness during the course of a pneumonic infection, and the deaths of his two siblings were also attributed to heart disease. It may therefore be significant for the patient under review that, in addition to the commonly occurring latent heart block, electrocardiographic changes suggestive of more serious damage were also encountered.

#### SUMMARY

A case of dystrophia myotonica has been described, with particular reference to its association with mental defect.

The author is indebted to Dr. H. S. Atkinson, Medical Superintendent of the Manitoba School, for permission to make use of institutional records and facilities.

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#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Pneumonia has probably been the object of more systems of treatment than any other disease, and yet, with all the accumulated experience of centuries, one is inclined to agree with Professor Osler that our results of treatment are probably no better than were those of Hippocrates. The statistical method of recording results was not born until long after the time of the father of medicine, but still Professor Osler's cynical statement has in it the elements of truth and is indeed humbling. Yet surely we have improved upon the days when pneumonia cases were routinely bled and given heroic doses of tartar emetic and purged

to depletion, as they were, probably, not in the days of Hippocrates, but rather in the more recent and violent days of the later centuries. Certain principles, at any rate, have been recognized within recent years, which must tend to the patient's good. In the first place, it is only within the last half century or so that the fact has been recognized that most cases of pneumonia tend to get better of themselves, and this knowledge of itself is a long step forward in the therapy of the disease.—Canadian Medical Association Journal, 1: 465, June 1911.

# CORRELATION OF CLINICAL, PATHOLOGICAL, AND BIOCHEMICAL FINDINGS IN A CASE OF CARCINOID TUMOUR\*

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CARCINOID TUMOURS have been shown to be the cause of a symptom complex that is due in part to their ability to produce 5-hydroxytryptamine (serotonin). They usually occur in the appendix, terminal ileum or cecum but may also be found in the rectum, stomach, or elsewhere. They are yellow-grey in colour and are made up of nests and columns of polygonal cells with deeply basophilic nuclei and a faintly acidophilic cytoplasm containing granules which stain with silver salts. They probably arise from the Kulchitsky cells of the glands of Lieberkühn. Invasion of the surrounding muscle layers and serosa or metastasis to regional lymph nodes and liver often provoke a massive fibrous reaction. Clinically, carcinoid tumours may present in a variety of ways, depending upon their site, the presence of metastases and their ability to secrete serotonin.

The following case illustrates features of a carcinoid tumour and the difficulty of confirming the diagnosis biochemically.

## CASE REPORT

A 71-year-old fireman was admitted to the University of Alberta Hospital with an eight-day history of crampy lower abdominal pain. Diarrhea had developed four days before admission and he became nauseated but did not vomit. Two similar episodes, each lasting about a week, had previously subsided without necessity for hospitalization. In the year before admission, the patient had lost 20 lb. and for 10 years had noted flushing after eating heavily. The colour of his face and neck, always ruddy, would increase in redness and his hands would develop red blotches. The flushes lasted half an hour and while they were present his skin felt hot.

On admission, this moderately obese, ruddy-faced man was in obvious distress from crampy abdominal pain. His blood pressure was 182/112 mm. Hg, his pulse rate was 96 per min. and was regular in rhythm; his temperature was 99° F. His chest was increased in anteroposterior diameter and was hyperresonant to percussion but there were no adventitious sounds. The heart sounds were distant and there were no cardiac murmurs. The heart was normal in size, clinically and radiologically. The abdomen was distended and generally tender, particularly in the right lower quadrant, where very



Fig. 1.—Radiograph showing the markedly distorted cecum and proximal ascending colon.

loud borborygmi were occasionally heard. Heavy pressure over a non-tender liver, which came down two fingerbreadths below the right costal margin, increased his facial redness.

Multiple attempts to fill the cecum with barium were unsuccessful because of colonic irritability but eventually barium and air contrast studies were completed which successfully demonstrated a cecal tumour associated with marked distortion of the colon (Fig. 1). Screening tests for the presence of 5-hydroxy-indole acetic acid (5HIAA) in the urine gave a faint pink colour. (When positive, this screening test is said to give a purple colour.)

At laparotomy a huge mass was demonstrated involving the cecum and terminal ileum and extending towards the mesenteric vessels and the



Fig. 2.—A photograph of the tumour. Note that it has surrounded the ileocecal valve. Small satellite plaques can be seen on the ascending colon.

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third part of the duodenum. This was shown to be a carcinoid tumour, 7 cm. in size, situated on the posterior wall of the cecum, stenosing the ileocecal valve (Fig. 2), and extending through the cecal wall to involve the distal third of an adherent retrocecal appendix. There were numerous satellite plaques in the ascending colon distal to the tumour. The lumen of the ileum was narrowed not only by kinking but also by thickening of the ileal wall. The regional lymph nodes were involved and the surrounding area showed considerable fibrosis. Metastatic involvement of the liver could not be demonstrated.

During the operative procedure, the anesthetist noted an episode of bronchospasm accompanied by generalized flushing. The postoperative course was uneventful and within a day the patient's skin colouring was normal. He volunteered the information that his "breathing was easier", although this had not been a complaint preoperatively and no wheezing was ever evident on auscultation. The urinary levels of 5HIAA are documented in Table I.

TABLE I.

Day	Urine 5HIAA mg./day
October 30.....	3
November 10.....	12
13.....	11
17.....	operation
19.....	1
21.....	4
23.....	1
24.....	4
26.....	2
28.....	1
30.....	2
December 2.....	6
3.....	5

## DISCUSSION

Basically, the symptoms associated with carcinoid tumours may be due to mechanical or to biochemical factors.

As the tumours commonly occur in the appendix, and obstruct it, acute appendicitis is a frequent preoperative diagnosis. Adhesions caused by the fibrous reaction may result in kinking of the bowel or intussusception and therefore the presenting picture may be one of intestinal obstruction. Radiological demonstration in the lower bowel often shows marked associated distortion. Rectal tumours may result in bleeding, constipation, tenesmus or pain.

Since serotonin is rapidly metabolized, principally in pulmonary and hepatic tissue, by monoamine oxidase, clinical symptoms of excess hormone are evident only when this biochemical barrier has been overwhelmed. Apparently this most commonly occurs when the tumour has metastasized to the liver.

The principal symptoms caused by elevated levels of 5-hydroxytryptamine (serotonin) are:

1. Flushing. This takes two forms: firstly, a persisting high colouring of the head and neck, and secondly, a transient blush of varying hues of red and blue. The latter usually lasts about 30 minutes, may be precipitated by meals, anxiety or posture, and is associated with a feeling of heat and with tachycardia or palpitations. Pressure over the liver may in some instances cause more transient flushing.

2. Gastrointestinal symptoms. As serotonin increases bowel motility, distension, loud borborygmi, colic or diarrhea may be present. The symptomatology also may be compounded by mechanical obstruction from the tumour itself.

3. Respiratory symptoms. Bouts of bronchospasm are manifested as transient attacks of asthma, sometimes associated with flushing.

4. Cardiac symptoms. Tricuspid and pulmonary stenosis or regurgitation occur owing to fibrosis of the endothelial surfaces of the right side of the heart. Heart failure may ensue and may be ultimately fatal.

Serotonin, through the action of monoamine oxidase, is oxidatively deaminated and appears in the urine as 5-hydroxy-indole acetic acid (5HIAA). The 5HIAA output in the urine accurately parallels an increased 5-hydroxytryptamine (serotonin) body level. The normal daily output of 5HIAA is between 2 and 8 mg., and a urinary excretion of 25 mg. or more has been considered strong evidence of the existence of carcinoid tissue. The whole blood 5-hydroxytryptamine level (entirely bound to platelets) is normally about 0.1 to 0.2 mg. per ml., with up to tenfold elevations in carcinoid patients, but technically it is much easier to determine the urinary output of the metabolite, 5HIAA.

The patient described in this report showed evidence of a physiological reaction to serotonin in three ways. Firstly, he had a persistent increase in facial colouring which subsided upon removal of the tumour tissue. (Episodic flushes were also present although not of the classically described polychromatic type.) Secondly, he gave suggestive evidence of bronchospasm and, finally, he exhibited irritability of the bowel which was demonstrated radiologically to be distal as well as proximal to his obstructing lesion. While most of his gastrointestinal symptoms were explainable on the basis of partial mechanical obstruction, such generalized hypermotility could not be explained on this basis.

The systemic effects of serotonin are presumably evident when the body level is such as to overwhelm the degradative ability of monoamine oxidase in the liver and lungs. In such cases high levels of 5HIAA should be demonstrable in the urine. Correspondingly, an inadequate supply of monoamine oxidase might be associated with symptoms. Here relatively low urinary levels of 5HIAA might be expected. Whether physiological effects can be produced by direct perfusion of serotonin from the tumour into adjacent tissue is not known.

In this patient, the laboratory results suggest that, despite the size of the tumour, its serotonin-producing capacity was low and symptoms therefore were evident only because the available supply of monoamine oxidase was also limited. Conceivably direct perfusion of the bowel by serotonin from the tumour tissue might also have played some rôle.

In Table I are shown the values for daily 5HIAA output before and after operation. The method used was the highly specific procedure of Udenfriend, Titus and Weissbach.<sup>1</sup> Known amounts of 5HIAA (Nutritional Biochemicals Co., Cleveland, Ohio), which was recrystallized until chromatographically pure, were added to normal urine to prepare a standard working curve. It is noteworthy that the highest preoperative level (12 mg./24 hrs.) is only slightly above the usually accepted normal range of 2 to 8 mg. However, a definitely significant fall to from 1 to 4 mg. occurred after operation. Minimal elevations of 5HIAA between 10 and 20 mg. per day have not been generally accepted as significant, although in Pernow and Waldenström's study<sup>2</sup> of the 5HIAA output of 22 patients with proven carcinoid, one patient showed a daily range of only 6 to 20 mg. (This patient was the only one in their group in whom liver metastasis was not demonstrated.) The screening method of Sjoerdsma, Weissbach and Udenfriend<sup>3</sup> is widely used to indicate qualitatively an increased output of 5HIAA in the urine. A purple colour is stated by the authors to constitute a positive test, occurring only when the urinary level of 5HIAA is above 30 to 40 mg./24 hours. In our preoperative series of tests, by this criterion no urine sample showed a

positive reaction, although one specimen gave a pink colour.

It seems obvious that cases such as the one reported here would be missed by this procedure. The sensitivity of the screening test can be increased two and a half times by simply changing the relative volume of sample to reagent as follows: 0.5 ml. urine, 0.5 ml. water, 0.5 ml. of L-nitrosodiphenol reagent, and 0.5 ml. nitrous acid. The rest of the test is carried out as described by Sjoerdsma except that the aqueous phase is shaken with ethyl acetate rather than ethylene dichloride. With this solvent, the purple colour (positive) appears in the lower (aqueous) layer. Levels as low as 8 mg./24 hours give a positive test with this simple change in procedure.

#### SUMMARY

The case history of a patient with a large carcinoid tumour which produced low levels of 5-hydroxytryptamine (serotonin) has been presented. Some of the clinical features of the "carcinoid syndrome" were present, but because there was only a slight increase in the urinary output of 5HIAA, the metabolite of serotonin, the screening test<sup>3</sup> commonly used for diagnosis was negative. By simply changing relative volume of sample and reagent used in the test it is possible to detect such minor increases of urinary 5HIAA.

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### CANADIAN JOURNAL OF SURGERY

The July 1961 issue of the *Canadian Journal of Surgery* will contain the following original articles, case reports and experimental surgery:

*History of Canadian Surgery*: Abraham Groves—C. W. Harris.

*Original Articles*: Enterocoele and prolapse of the vaginal vault—K. T. MacFarlane and D. E. R. Townsend. Acute surgical disease of the abdomen complicating pregnancy—R. A. Macbeth. Rupture of the liver in children: a 34-year review at the Hospital for Sick Children, Toronto—S. A. Thomson and N. W. Mortimer. Report of 41 cases of rupture of the spleen—F. G. Fyshe and S. E. O'Brien. Traumatic hemobilia—J. C. Fallis and C. A. Stephens. Spontaneous rupture of the esophagus—N. T. McPhedran. L'infiltration périurale continue dans les fractures multiples de côtes—M. Trahan and F. Hudon. Excision of the carpal scaphoid for ununited fractures—H. S. Gillespie. Experience in the surgical management of duodenal and gastric ulcers—A. J. Grace. Carcinoma amongst Labrador Eskimos and Indians—G. W. Thomas. Basal cell sarcoma—S. Gordon.

*Case Reports*: Massive hemorrhage due to diverticular disease of the colon: a case illustrating the bleeding point—I. Salgado, G. K. Wlodeck, W. H. Mathews and H. Rocke Robertson. Rupture and stenosis of mainstem bronchus—R. H. Craig. The tibialis anterior sesamoid—R. A. Haliburton, E. G. Butt and J. R. Barber.

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## MEN AND BOOKS

### EDINBURGH AND CANADIAN MEDICINE: THE FIRST ALEXANDER GIBSON MEMORIAL LECTURE\*

#### PART I

SIR WALTER MERCER, D.L., M.B., Ch.B.,  
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F.R.C.S.(I)(Hon.), F.R.C.S.[C](Hon.),  
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ON THIS occasion we are met together to pay tribute to one of the greatest pioneers in orthopedic surgery, to one who is revered in this university, and to one whose reputation extends far beyond the boundaries of Canada. It is to me a very special privilege and honour that I am chosen to speak on your behalf and to submit the first Alexander Gibson Lecture—a special honour because not only is his own Alma Mater in Edinburgh but orthopedic surgeons the world over hold him in such high regard as a man of outstanding distinction. It is, then, perhaps not inappropriate that this first lecture should be given by the first occupant of the Chair of Orthopaedic Surgery in Edinburgh.

Alexander Gibson was born in Edinburgh in 1883. He was a medical student at Edinburgh University where he graduated in 1908 with first-class honours, being awarded the Ettles Scholarship as the most distinguished student of his year. He established a remarkable record—he was the first student in the history of the University to earn all the scholarships available to him during his course. In 1913 he took the Fellowship in Surgery of the English College, and later in the same year he came to Winnipeg to become Professor of Anatomy in Manitoba Medical College.

The First World War broke out a year after his arrival and he saw service in India and Egypt and was on board a transport torpedoed in the Mediterranean. Later he was appointed to the Chair of Orthopedic Surgery in the University of Manitoba. During the Second World War he returned to Scotland to take charge of a Canadian Red Cross Hospital at Hairmyres.

Many honours were conferred upon him and among this long list were the Fellowship of the Royal Society of Edinburgh, Presidency of the Canadian Orthopedic Association, and Fellowship of the American College of Surgeons. He liberally poured out his rare and precious gifts in favour of Canada, and a number of his publications are of lasting significance. He was the first to demonstrate

that the menisci of the knee regenerate following operative excision. The "fish-tail" graft introduced the principle of an interlocking graft in spinal fusion. Probably his most important contribution was the posterolateral approach to the hip joint now widely used by orthopedic surgeons. He preferred to call this a "modified Kocher incision" although it was original in concept.



Sir Walter Mercer

Gibson was never spectacular but everyone trusted him and everyone liked him. His work was done quietly and unobtrusively, but always with the greatest efficiency. Indeed, his obvious sincerity and effortless charm won for him a universal measure not only of regard but of affection. He had quite a sense of humour. When he went to do a locum in Lanarkshire he said to his chief on his way to bed "Should I take off my boots, do you think?" He suggested that should there be an emergency he would save time by sleeping as he was. This was told me by his then chief, Dr. Douglas Guthrie, who did not realize that he was having his leg pulled.

One of the most characteristic traits in his character was an instinct to do gracious little things which most people would never even have thought of but which meant so much. He was amiable, thoughtful, and considerate and very sensitive in his reactions to other people's circumstances and feelings.

Some thought him cold and aloof, but in fact he was retiring by nature and humble of heart, and disliked all forms of publicity. He was sensitive and shy, and participation in public affairs meant a heavy strain upon his nervous energy. Loyal to duty and faithful in the discharge of it, he burned himself out long before his time.

Notwithstanding his crowded and arduous years he found time for the cultivation of his own mind and soul. He loved the countryside and healthy sport and simple things, and in music he could completely lose himself and forget worldly cares.

\*Delivered at the University of Manitoba, Winnipeg, Man., January 17, 1961. This is the first of two instalments in which this lecture is being published. The complete bibliography will be published with Part 2.  
†Past President, Royal College of Surgeons, Edinburgh; Emeritus Professor of Orthopaedic Surgery, University of Edinburgh.

His mind was richly garrisoned—a delicate scholar, a tireless reader, avid and eager to the very end, original, constantly making worthwhile discoveries in lonely and little-known spots in literature far off the beaten track.

His mother was a wonderful old lady, alert in mind and full of pawky humour. One evening someone said to her—"How proud you must be of your son", to which Mrs. Gibson, obviously bursting with pride but with characteristically Scottish restraint determined not to show it, replied, "Yes. Alex has done quite well. But, of course, he will never be the man his father is."



Dr. Alexander Gibson

There was never anything aggressively Scottish in his accent, outlook, or temperament, yet he was sturdily loyal to earlier objects of his reverence and he forfeited nothing of what he had derived from the influence of his native soil.

In February 1956, about a month before he died, Gibson was invited to join a team of doctors who flew far north into the wilderness and stayed for a week to study congenital dislocation of the hip in Indian infants—a subject which had been for him a life interest. One hundred children were brought in from distant northern points and examined. The doctors stayed at a Roman Catholic mission station at Island Lake. The temperature was very low outside and it was almost equally cold inside. Gibson had just returned a few days before from Mexico, where the heat was very trying. Many have thought that this trip was a contributory factor in his last illness, but Gibson was game to go anywhere and try anything to further progress in medical science, and particularly in the orthopedic aspect of it.

His was a life lived out and a rest thoroughly earned. Working to the last, the blow fell and he was gone, spared the long agony and pain and helplessness through which so many have to reach this hard-won goal.

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In the early days of what we might call learned medicine there were many graduates of Edin-

burgh, many who had taken classes in Edinburgh but qualified elsewhere, and many postgraduates who had studied in Edinburgh, but all of whom in time had proceeded to North America and left some mark on medical history there.

During the latter half of the 18th century Edinburgh was the great medical resort of all Britons beyond the seas, much as Leyden had been half a century earlier. In the century following 1765, when the Edinburgh Medical Faculty had been in existence for forty years, 650 students from the Americas, including Canada and the West Indies, graduated in Edinburgh. One hundred and four Canadian-born students had graduated M.D. at Edinburgh by 1867. A larger number took a few classes after getting a degree elsewhere, or took the licentiateship of the Royal College of Surgeons of Edinburgh—the oldest College in the world, chartered in 1505. This influence began in Canada at about the time of the transfer of Canada to British rule in 1763. Many of the army surgeons were of the Scottish school; several settled in the country.

So I hope to show that the influence of Scottish medical training on the development of Canadian medicine in its early days has been quite considerable.

But it was not a Scot who was the first medical man to emigrate to America. I will mention two medical men who were not Scots.

Many years before the founding of the colonies on the Atlantic side of North America the continent was visited by a British doctor on the Pacific side. The search for El Dorado and a short passage to the Indies led the doughty seamen of the 16th century to sail the Spanish main, and even round the Horn. A British surgeon accompanied Sir Francis Drake, the "patriot pirate" as he has been called, on the *Golden Hind* and reached what is now Northern California in the year 1579. This man's name was THOMAS HOOD. Of course, he was not the first physician of any country to reach America, in which we include the West Indies. For, lest we of British blood feel uppish about the part our race played in the development of America, we should remind ourselves that the Spanish had founded a hospital in Mexico in 1524.

Perhaps the first medical man to emigrate to America would be SAMUEL FULLAR. Just about three centuries and a half ago a little sailing vessel was struggling against adverse winds and heavy seas towards America. On board were one hundred pilgrims fleeing from civil and religious tyranny to seek sanctuary and freedom in a new land. No voyage in history has been so fateful. Those who journeyed in that vessel, a chosen company, were the best of the home stock. They helped to found here a small colony of people, grim and stoical in character, yet touched with idealism. And in that little boatload was Samuel

Fullar, the first practising physician to visit the British colonies in North America.

The great migration from Scotland began in the 17th century, especially during the reign of Charles II, and a century later the exodus was in full flood. In the thirty years preceding the American revolution Scotland's sturdiest sons were going west in boatloads. Eventually the number of those immigrants averaged 12,000 a year. Religious intolerance, economic repression, the Jacobite rebellion, and, later, the Highland clearances, all helped to fill the emigrant ships. North America was a refuge—and an opportunity.

It is a continuance of this influx—because of it, though for very different reasons—that men of medicine in the following centuries migrated to the U.S.A. and Canada, and so they have left their mark on the profession and, indeed, far afield of it.

In a country now so vast and variously peopled it would be impossible to determine the exact extent of Scottish influence, but regarding the foundation times, where the scene is more clearly defined, it is easy to remark the Scottish impact.

#### QUEBEC

From the little that is known of the first medical men to arrive in Canada they seem, with a few exceptions, to have been barber-surgeons and apothecaries. They came in the first instance with Champlain on his voyage to Quebec and later with the troops and colonizers for New France.

By the beginning of 1700 it is said that about 96 people practising medicine were scattered along the St. Lawrence up to Montreal. Many of these can have been little better than charlatans.

The surgeons of Canada of those early days had no degrees. Surgery occupied a very inferior status socially and scientifically; the surgeons had for their associates, barbers, and they practised conjointly with them and performed bleeding and minor operations. This fraternity was sanctioned by Royal assent and letters patent in 1613. It was not essential that one be apprenticed to a surgeon or that one obtain degrees; it sufficed that one settled in the country to enjoy the privilege of the practice of any of the professions.

The first medical men in what is now the Province of Quebec who were not native Indians were mostly Frenchmen trained in France, but ADAM MABANE seems to be the earliest of the doctors referred to in Maude Abbott's "History of Medicine in the Province of Quebec" who settled there. He was born in Edinburgh in 1734 and received his education there. Mabane came to Canada as surgeon's mate on the hospital staff of General Amherst in 1759, just a few days before Quebec was captured. He stayed on at Quebec and became known as a famous physician and practised there until his appointment as a judge in 1764, though he still continued as surgeon to

the garrison from 1766 till 1783. He was one of the founders of the Quebec Library Association.

Among the Quebec physicians who were associated with the mal de la Baie St. Paul there were Badelard, Lathan, Mabane, Nooth and Bowman.

BADELARD may be mentioned for his contact with a good Scotsman, FRASER. Badelard was present at the battle of the Plains of Abraham and, seeing that the French were fleeing, turned to do the same himself when he found himself faced by a giant Scottish Highlander. Badelard presented his revolver but the Scot brushed it aside and made him prisoner. After peace was declared Badelard practised in Quebec and Fraser opened a school and the two thereafter became fast and lifelong friends.

Badelard was in time succeeded by J. MERVIN NOOTH in investigating Baie St. Paul disease and is said to have made an able report on the outbreak. Nooth graduated M.D. from Edinburgh in 1766. He wrote an article to Franklin on "Some Improvements in the Electrical Machine" and was made a Fellow of the Royal Society in 1774.

NOOTH was appointed Physician Extraordinary to the British Army in North America in 1775 and served in the War of Independence. He returned to Britain, but when Lord Dorchester came out in 1786 to be Governor of Quebec again, he brought Nooth with him as superintendent of hospitals in Quebec.

The Lieutenant-Governor of Upper Canada, Simcoe, was anxious to tap the "Salt Springs" between Lakes Huron and Ontario and he wrote—"Dr. Nooth has been so obliging as to direct the mode of investigation and to apply his eminent talents to forward what may prove of such public benefit."

Nooth eventually retired to England because of asthma and there wrote an article "Case of a Disease of the Chest from a Lead Shot passing through the Glottis into the Trachea", which was autobiographical. A large shot about 1/8" in diameter in the last glass of a bottle of wine which about two years before had gone down the wrong way, was coughed up by him soon after his arrival in London in 1799 and his asthma soon disappeared.

About the year 1773 the attention of the Government of Lower Canada was drawn to the increasing ravages of a peculiar disease which, originating at Baie St. Paul, had spread to other parts of the province. A tradition exists that it was imported into Baie St. Paul by a detachment of Scottish troops, so the influx of things Scottish was not limited to the immigration of doctors. Heagerty lets us out later, however, for he says there is much reason to doubt the correctness of this supposition.

At any rate it was a particularly loathsome disease, characterized by ulcers, glandular swellings, and disease of the bones. The ulcers of the face were so extensive that every part of the face might

disappear. Dr. Nooth, who had a great deal to do with the investigation of the disease, wrote that it was nothing more than venereal disease aggravated by neglect.

Although one doctor noted its resemblance to "Gibbens", the gaelic name given to syphilis in Scotland, one is pleased to note that Swediaur wrote "They call it Mal Anglois because they think the English brought it first among them . . . and where it is of more modern date they call it La Maladie Allemande."

The Province at this time had no facilities for teaching medicine other than the form of apprenticeship which did not appeal to the ambitious student. It was necessary to go elsewhere for a medical education. One of the earliest students to go abroad was JACQUES LABRIE who, after serving an apprenticeship locally, went to Edinburgh to complete his studies. He was the first to visit and study at the "Royal" University there, so writes Birket in 1908. Before leaving for Edinburgh, Labrie founded a newspaper called "Le Courier" which announced his return to his native city in 1808. Some time thereafter he entered politics and became a member of the Chamber of Assembly; and it is to him that the profession is indebted for the institution of those tribunals which now guard the honour of the medical profession.

As regards medical teaching in Quebec a meeting of medical students of the Marine Hospital in the city was held as far back as 1835 to discuss the question of medical education, and they recommended that a School of Medicine be established.

The Marine Hospital was founded by DR. JOSEPH MORIN, who was the first Professor of this School. He had been born in Dumfriesshire, Scotland, in 1794, brought by his parents to Canada at an early age, and had afterwards returned to Edinburgh to study medicine.

The year 1826 marked an era in the history of medicine in Quebec. It gave birth to the first attempt to open a free intercourse with the literary world and to promote interest in and cultivate medical science by the formation of the first Medical Society in Quebec. The President was JOSEPH MORIN. It was at the same time and under similar auspices that the first medical journal in the province appeared.

In 1852 the teachers in the Incorporated School of Medicine were formed into the Medical Faculty of Laval University. Out of the original Faculty of five professors, one, J. A. SEWELL, was an Edinburgh graduate and became Professor of Internal Pathology and Special Therapeutics.

#### MONTREAL

The first Canadian School of Medicine was founded by James McGill, a graduate of the University of Glasgow, who had settled in Montreal when it was a little town of 9000 inhabitants. He left a share of his fortune for the foundation of a

hospital when he died in 1813. Its Medical Faculty was founded, as to its organization and methods of teaching, on the Edinburgh school. The Royal Charter was granted to the Royal Institution for the Advancement of Learning and to McGill University in 1821 by George IV.

The first Professor of Medicine on the staff of the Faculty was a THOMAS FARGUES, an Edinburgh graduate. Actually, however, the University then existed only on paper and Fargues' position was purely nominal. It was not until 1828 that the Faculty emerged from its state of suspended animation.

IN 1821, THE BUILDING OF THE MONTREAL GENERAL HOSPITAL was commenced and the foundation stone was laid with great ceremony. The new building cost £5856 and contained 100 beds. In 1823, four medical men had formed a private medical school in Montreal—the Montreal Medical Institute—the first of its kind in the country. These men formed the medical staff of the newly built Montreal General Hospital founded in 1819. This School flourished, but it was never granted the right to confer degrees, since it was not affiliated to any teaching institution. After unsuccessful attempts to obtain a charter, the staff of the School was appointed to McGill University and so the latter acquired an active, well-qualified Faculty of Medicine.

The medical staff consisted of Drs. Holmes, Stephenson, Robertson and Caldwell, also Drs. Lordel and Lyons. The first four were Edinburgh men. The charter was strongly opposed by a Mr. O'Sullivan. Dr. Caldwell wrote a strong letter to the "Courant" to which he did not sign his name. Mr. O'Sullivan said in the House that if the writer would declare himself, i.e. sign his name, he would call him out. Dr. Caldwell next day wrote a stronger letter under his own name and was, consequently, called out by the legislator. They exchanged five shots. O'Sullivan was shot through the chest, and Caldwell had his arm shattered. In those days they fought with pistols carrying an ounce bullet. Both recovered, O'Sullivan after a prolonged and critical illness.

No sooner was the hospital in good running order than the staff determined to start a medical school, and Holmes and Stephenson were appointed to form a committee to enquire into the matter. One week after this committee was appointed certain resolutions were adopted to promote this desirable object. Amongst these resolutions, number five stated:

"They were encouraged to attempt the formation of a medical seminary when they reflect that the Medical School of Edinburgh, now justly considered the first in Europe, the basis of which they would adopt for the present institution, is of comparatively recent formation, it being little more than 100 years since medical lectures were first delivered in that city. The early history of the Edinburgh Infirmary is not dissimilar to that of the General Hospital."

The resolutions were approved by the Governor General, Lord Dalhousie, a Scot, and in the autumn of 1824 lectures and clinics were commenced, with a class of 25 students. The school was called the Montreal Medical Institute and was more or less at that time a private enterprise. There was much similarity between the Edinburgh Infirmary and the Montreal General Hospital.

After some formalities the Institute became the Faculty of Medicine of McGill College, but one lecturer only had the rank of Professor—Dr. Andrew Fernando Holmes. Thus again was the resemblance to Edinburgh continued, for in 1725 the extramural Medical School of Edinburgh became the Medical Faculty of Edinburgh University. In 1825, however, all the lecturers were made professors.

Great credit is due to the founders of the School whose foresight, energy, perseverance, and great ability made it possible. Dr. Holmes (1797-1860) and Dr. Stephenson (1797-1842) were both graduates of Edinburgh University. Dr. Robertson (1784-1844) and Dr. Caldwell (1782-1833) were retired Army surgeons, also educated in Edinburgh. To those four was soon added G. W. Campbell, a graduate of Glasgow, who was appointed Professor of Surgery in 1833 and held the Chair until 1875. Robertson was a Scotsman, born in Kendrochet, Perthshire. He was educated in Edinburgh and joined the 49th Regiment as Assistant Surgeon, and fought in the war of 1812-14. Caldwell, also a Scot, born in Ayrshire in 1782, graduated in medicine at Edinburgh and was surgeon to the 13th Dragoons and served in the Peninsular War.

STEPHENSON WAS THE ONLY BORN CANADIAN of the four and was educated in Montreal, and in medicine in Edinburgh. He came of a family who held a good position, his father being a merchant in the city of Montreal. The family had been in Canada since the year after *the conquest*. His Edinburgh graduation thesis "*De velosyn-thesi*" is in the Osler library. It was a description of his own case. He had been operated on by Roux of Paris and apparently was the first instance of his operation done for cleft palate.

HOLMES WAS BORN IN CADIZ, Spain, and would have been born in Canada had not chance prevented it. His family were coming out to Canada in the latter part of the 18th century when the ship on which they sailed was captured by a privateer and brought into Cadiz as a prize. They were detained there several years and there Andrew Fernando Holmes was born—hence his name, Fernando. He was four years old when he came to Canada. He was a man of wide interests and of great mental power. His name recurs in the Annual Award of the Holmes Gold Medal to the student at McGill with the highest aggregate of marks in the medical course.

In 1813 Holmes and Stephenson went together to study medicine in Edinburgh and graduated from that University in 1819. Drs. Robertson and Caldwell, having retired from the Army, were also

established in Montreal, and these four men were the ones who were chiefly instrumental in stimulating the rich merchants to provide funds for the establishment of the General Hospital.

The Chairs they held were:

Dr. Stephenson—Anatomy, Surgery and Physiology.

Dr. Holmes—Chemistry, Botany and Pharmacy.

Dr. Robertson—Midwifery.

Dr. Caldwell—Practice of Physic.

In 1832, when a Royal Charter was obtained, Thomas Fargues, an Edinburgh graduate, was elected Professor of Medicine. From this small beginning the University of McGill College rapidly increased so that it numbered 108 medical students in the year 1860, and ultimately became one of the most famous schools of the western hemisphere.

A well-known and eminent physician was Dr. James Stewart. He was Professor of Medicine in McGill University and senior physician to the Royal Victoria Hospital. Although graduating from McGill in 1869, he went on for further study in Edinburgh and was admitted there L.R.C.P.&S. in 1883. He was President of the American Association of Physicians and at one time Secretary of the Canadian Medical Association.

L'UNIVERSITÉ DE MONTRÉAL, which was incorporated in 1920, was the product of the union of L'Ecole de Médecin et Chirurgie de Montréal, the first French medical school to be established in Montreal, and L'Université de Laval.

L'Ecole de Médecin et Chirurgie had been founded in 1843 by a group of medical practitioners, including men of great distinction in Canadian medical history—Drs. Arnoldi, Francis Badley, Munro, Sutherland and McNider. Dr. Francis Arnoldi, the first President of the School, had graduated M.D. at Edinburgh in 1827. Dr. Francis Badley had graduated M.D. at Edinburgh in 1829. Dr. Pierre Munro was of Scottish descent from the family of Munro of Foulis, the same family as that of Edinburgh's famous Alexander Munro. Dr. Wm. McNider had graduated M.D. at Edinburgh in 1836 and in addition to lecturing on obstetrics in L'Ecole de Médecin was one of the founders of the old Lying-in Hospital, later called the Montreal Maternity Hospital.

Dr. Hector Peltier, who had graduated in Edinburgh in 1845, was later appointed Professor of the Institute of Medicine. This school began as a protest against what was said to be a monopoly of teaching and hospital appointments by McGill, but later several of its staff received appointments at McGill.

#### UPPER CANADA

Even as late as 1815 there were not more than 40 qualified men in Upper Canada. Quacks flourished. An appeal is found in a Kingston newspaper against quacks "who without one ray of science, presume to thrust the created into the presence of the creator".

## ONTARIO

The first doctors in Ontario were surgeons of British regiments who cared for the civilians living close to the garrisons. Later some of those men retired from the Army and remained to do civil practice only.

The most important military medical man in the earliest days of Ontario was James McCauley, who had been born in Scotland in 1759. He held both the M.D. and the M.R.C.S.E. He came out to New York in 1779 and was surgeon's mate to the Queen's Rangers. A great friend of his was Col. John Simcoe, who was in command of the Queen's Rangers during the American Revolution, and when Simcoe arrived as the first Governor of Upper Canada in 1792 he induced McCauley to join him. Later McCauley was made Deputy Inspector-General of Hospitals of the Province and lived at the capital, York, when the place was first settled. His own name, that of his wife and other members of his family are commemorated in the street names of the district early known as McCauley village, and later as St. John's Ward. He took a prominent part in the affairs of York and was Senior Member of the Medical Board of Upper Canada. McCauley's assistant in the Queen's Rangers was an Irishman, Dr. John Gamble, an Edinburgh graduate of 1793. Gamble settled in Kingston when the regiment was disbanded about 1802 and there afterwards had a large practice.

Dr. William Warren Baldwin was the first civilian doctor to settle at York about 1800. He was born near Cork, Ireland, took his M.D. at Edinburgh in 1797 and, after practising for a year or two in the old country, came out with his family and settled in the township of Clark, Upper Canada. Besides practising medicine at York, Dr. Baldwin started a small school for boys and also became a prominent lawyer. On one occasion it is said he had to interrupt his pleading in court to deliver a woman in labour, thus establishing an early Canadian precedent for the pre-eminence of medicine over law. It must have been unusual to have to double his parts like this, as they were healthy folk in those days. Indeed, a contemporary Toronto poet, A. J. Williamson, says:

"The doctors only pine and dee  
For want o' work in Canadie."

Dr. Baldwin's house in Toronto gave the name to Spadina Avenue in that city. He had dreams of establishing a family in Canada with an entailed estate; there was to be always a Baldwin of Spadina. But by the irony of fate his eldest son, Robert, who eventually became Attorney General, was to carry through the Dominion Parliament abolition of the rights of primogeniture and the right of succession to the first-born.

These three Edinburgh graduates, McCauley, Gamble and Baldwin, are said to have exerted a wide and salutary influence socially and profession-

ally on the medical interests of York and the province in general.

Another interesting pioneer physician of Ontario was Dr. Wm. Dunlop, who practised in York in the early days. In early life he was a surgeon in the Connaught Rangers and was actively engaged in the campaigns of 1813-15 against the Americans. When he lived in Edinburgh he gave a course of lectures on medical jurisprudence and published an edition of Beck's Medical Jurisprudence as well as a book called "War of 1812".

Perhaps the most extraordinary thing he did was the will that he drew up. He starts off by saying "Being in sound health and my mind just as usual, which my friends who flatter me say is no great shakes at the best of times" . . .

Amongst the items are—

"I leave my silver tankard to the oldest son of John, and would have left it to John himself but he would melt it down to make temperance medals."

"I leave my brother Allan my big silver snuff box as I am informed he is rather a decent Christian with a swag-belly and a jolly face."

"I leave parson Chavasse (Maggie's husband) a snuff box as a token of my gratitude for the service he has done the family in taking a sister no man of taste would have taken."

"I leave John Caddle a silver teapot to the end that he may drink tea to comfort him from the affliction of a slatternly wife."

## TORONTO

The Faculty of Medicine of Trinity College in 1850 consisted of six professors. Of these the best known was Dr. JAMES BOVELL. Dr. Bovell who, along with his colleague, Dr. Hodder, helped in the foundation of the Trinity Medical Faculty, was a very interesting man. He was born in the Barbadoes in 1817 and studied medicine in Edinburgh. He came to Canada in 1848 from Barbadoes where he had been in practice, and settled in Toronto where he soon acquired a large connection. He became Professor of Medicine and Dean of the Faculty, and in 1857 assisted in the foundation of the *Upper Canada Medical Journal*, the first medical journal published in the province. The Bishop of Antigua urged upon him the duty of taking orders, so great was his influence for good among all classes. He accordingly spent the rest of his life as a missionary in the West Indies. He was known as "the beloved and saintly James Bovell".

A man who occupied a unique position in the surgery of Toronto was ALEXANDER PRIMROSE. He came to Toronto from Nova Scotia, a young man in his twenties, and achieved eminence as a pathologist, an anatomist, a surgeon, a teacher, a soldier and as a leader in organized medicine.

He used to say that he was "kicked into surgery", for as a result of a kick he had a broken leg and was

under the care of John Stewart of Halifax. Alexander Primrose's contact with Stewart opened his eyes to a vision fascinating to a young man, for then the whole world of medicine was being revolutionized by antisepsis. He went to Edinburgh where he graduated M.B., C.M., in 1886 and two years later began his great career in surgery in Toronto. It was as Professor of Anatomy there that he made one of his greatest contributions to medical teaching. He was ambidextrous and illustrated his lectures by drawing diagrams of anatomy in colour with both hands. His lectures were a combination of lucid description and these beautiful diagrams. He later held the Chair of Clinical Surgery and in that position was well able to transfer his enthusiasm to his students. He was in Salonika in the great war as officer in charge of surgery with the Toronto General Hospital. He held many important positions in Canadian surgery but he went further afield and was President of the American Surgical Association in 1931. The greatest tribute to his administrative ability was his appointment as Dean of the Faculty of Medicine of the University of Toronto in 1920. We are proud that another Edinburgh-trained man now holds that position—Dr. J. A. MacFarlane.

Many honours came to Alexander Primrose. The Royal College of Surgeons of England elected him a Fellow in 1925. His Alma Mater, the University of Edinburgh, awarded him an LL.D. in 1926, and Dalhousie University the same degree in 1930. He reached the rank of Colonel in the Army and was awarded the C.B. for his services. He was a man of great character who for a long time wielded a powerful influence for good upon the surgical and social life of Toronto and Canada.

One of the Edinburgh men who came to Toronto at the beginning of the century and made his mark there, and elsewhere afterwards, was B. P. WATSON. He was the first scholar of his year and an honours graduate from Edinburgh in 1902 and took a gold medal for his M.D. in 1905.

He was appointed to the first Chair of Obstetrics in Toronto in 1912 and was known for the quality of his teaching no less than for the brilliance of his operating, and so was much sought after as a consultant. He was a pioneer in gynecological pathology and an author, in conjunction with Freeland Barbour, on the subject. Although a strict disciplinarian and with rather a brusque manner, these were overshadowed by the many little acts of personal kindness for which he was so well known. He came back to Edinburgh in 1922 to the Chair of Obstetrics but retained it for only four years, as the greater opportunities and broader outlook in the Presbyterian Hospital of New York tempted him too strongly. And there in New York he still is and, although retired from hospital practice, his home is a mecca for Edinburgh men, and I daresay Toronto men too.

(To be concluded)

## REVIEW ARTICLE

### PLACENTA PREVIA ACCRETA: REVIEW OF THE LITERATURE AND REPORT OF A CASE

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**PATHOLOGICAL ADHERENCE** of the placenta, or placenta accreta, in combination with placenta previa is a rare but serious complication of pregnancy. It was first reported by Plater,<sup>1</sup> who cited the case of Galla, a noble lady who was delivered on March 25 in the year 88 A.D. The afterbirth was retained and the patient died. On opening the body the placenta was found to be firmly adherent about the internal os. Morgagni<sup>2</sup> reported a case in which the patient died with the placenta undelivered after fever and rigors. At autopsy the placenta was found *in situ* partly over the internal os and partly at the fundus and so firmly attached that it could be separated only with difficulty even with a knife.

A recent personal experience prompted the author to discover what had been done by others when confronted with the problems of such a combination. A search of the records of the Winnipeg General and St. Boniface Hospitals over the past 10 years, representing somewhat over 50,000 deliveries, failed to reveal a pathologically proved case, although there were several which were clinically suggestive. In 1952, Kistner, Hurtig and Reid<sup>3</sup> published an excellent review on the subject including data on 21 collected cases and nine of their own. Since then approximately 30 cases have been reported, most of which have been available to the author.

#### INCIDENCE

It is impossible to reach a reasonable estimate of the incidence of the combination of placenta previa and placenta accreta. This is largely due to the lack of agreement regarding diagnostic criteria for placenta accreta. The reported incidence of placenta accreta varies from one in less than 2000, reported by Irving and Hurtig,<sup>4</sup> to zero occurrence of total placenta accreta in approximately 70,000 deliveries at the Johns Hopkins Hospital, reported by Eastman.

#### CLASSIFICATION

Several classifications of the degree of placenta previa are currently in use and are well known. With regard to placenta accreta the two classifications described by Aaberg and Reid<sup>6</sup> in 1945 are usually followed. They classify placenta accreta:

1. With regard to the degree of lateral involvement as (a) Total; (b) Partial—representing pathological adherence involving one or more cotyledons;

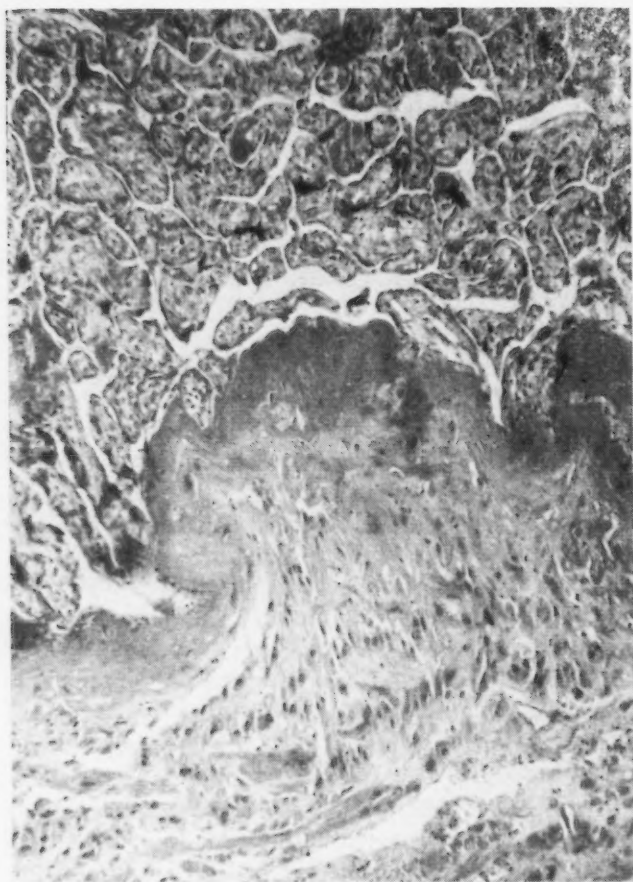


Fig. 1.—Placenta accreta. Chorionic villi are directly adherent to the underlying myometrium which is superficially hyalinized.



Fig. 2.—Placenta accreta. Direct extension of distorted chorionic villi into endothelialized channels within myometrium is seen.

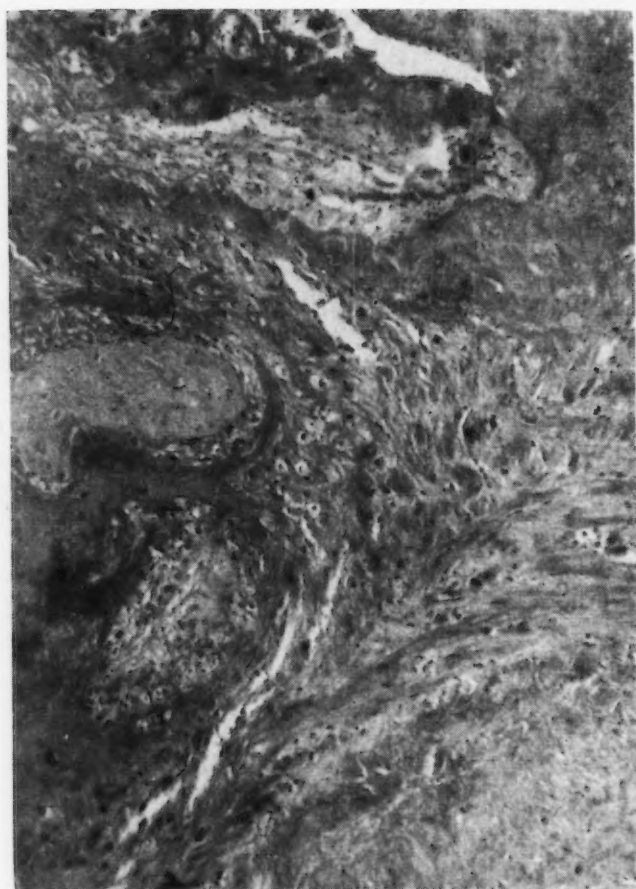


Fig. 3.—Placenta accreta. Fibrosed chorionic villi are surrounded by myometrial smooth muscle fibres.

(c) Focal—where only part of a cotyledon is involved.

2. By depth of involvement as (a) Accreta—adhering to the uterine walls; (b) Increta—penetrating into the musculature of the uterus; (c) Percreta—penetrating the thickness of the uterine wall.

#### PATHOLOGY

The histological pathology pertaining to placenta accreta was well described by Irving and Hurtig<sup>4</sup> in 1937 and more recently has been studied extensively and reported by Millar<sup>7</sup> in 1959. The most conspicuous aberration from the normal is the partial or complete absence of the decidua. It is this which probably accounts for the abnormal adherence of the placenta to the uterine wall, as in the normal implantation the spongy layer of the decidua basalis affords a plane of cleavage. The myometrium shows increased vascularity, especially in the superficial layers, and these muscle fibres often show a considerable degree of hyalinization. The combination of increased vascularity and increased hyalinization makes it easy to understand the excessive hemorrhage which occurs when such a placenta is forcibly detached. Abitol, Daichman and Mackles<sup>8</sup> suggest a third cause for bleeding, namely, the lack of thromboplastin-rich decidua.

### CASE REPORT

Mrs. A.W. (No. B36815), aged 32 years, para 3, gravida 6, was admitted to St. Boniface Hospital on June 28, 1959, in active labour.

In 1951 she had an appendectomy; otherwise there was nothing of note in her past history of illnesses. In regard to family history, one sister had several premature children.

### Obstetrical History

In October 1952, she had a normal pregnancy and delivered a normal female at term after a relatively easy labour.

In June 1953, she had an abortion at less than three months.

In March 1954, she was hospitalized several times for back pain during pregnancy. At about six months premature twins were born. There was no bleeding during pregnancy, but there was enough hemorrhage associated with the delivery that she was given two bottles of blood. The patient thinks that the afterbirth was not situated properly. (As these pregnancies occurred in Germany, the details cannot be readily corroborated.)

In July 1955, her fourth pregnancy occurred in Canada. During the third month she was hospitalized for a possible ectopic pregnancy because of pain but no bleeding. After this the pregnancy continued normally and she delivered a normal male weighing 7 lb. 4 oz. at term, after a labour lasting only 20 minutes.

In October 1955, she had an early abortion for which she was curetted to control the bleeding.

### History of Present Pregnancy

Her last normal menstrual period was September 16, 1958, and her expected date of delivery was June 23, 1959.

The duration of gestation at the time of delivery was 40 weeks.

In November 1958, when two months' pregnant, she was admitted to hospital because of threatened abortion with bleeding but this settled down when she was kept at bed rest and given analgesics and progesterone.

In February 1959, when approximately five months' pregnant, she was again admitted with the diagnosis of threatened abortion. At this time the bleeding was heavy enough on admission for the patient to be in shock. She was treated by administration of analgesics, progesterone and two blood transfusions and was discharged after four days in hospital.

After this the patient continued to have lower abdominal and groin pains throughout the rest of her pregnancy. She saw her doctor at least ten times, gained a total of 30 lb. and was given an iron preparation, and towards term, because of insomnia, was given sedatives.

On June 16, 1959, she was admitted complaining of constant lower abdominal pain and back pressure, apparently thinking she was in labour. Her blood pressure was 110/58, fetal heart sounds were present, the membranes were intact, and there were questionable irregular contractions. These contractions stopped after several hours. On June 17, because of the severe pain and poor obstetrical history, a medical induction

was decided upon. This produced a few contractions but did not result in effective labour, so she was discharged June 18, still pregnant.

### Labour and Delivery

On June 27 at 11 p.m. labour began. She was admitted on June 28 at 2 a.m.. Her blood pressure was 112/70 and fetal heart sounds were 160/min. Her membranes were intact. Contractions were every 5 to 8 minutes, fairly mild. Progress was described as "slow". At 4.15 a.m. she had a large amount of bleeding, approximately 150 to 200 c.c., with some clots. The cervix at this time was thinning and 1½ fingers' dilated; the presenting part was high and the membranes were intact. The blood pressure was 105/70. Fetal heart sounds were 160/min. At 5 a.m. she was described as "bleeding profusely", having lost 450-500 c.c.; she complained of headache and of not feeling well. She was taken to the case room and at 6.03 a.m. was delivered spontaneously of a living boy (vertex presentation, left occiput anterior) weighing 6 lb. 3½ oz.; Apgar rating was 3. The duration of the first stage of labour was 6 hr. 45 min.; the second stage, 18 min.

The baby's condition improved rapidly.

As the placenta failed to separate, a manual removal was performed but with difficulty. Bleeding continued during this time from the placental site which could be seen fairly easily in the lower segment posteriorly. Ineffectual efforts were made to control the bleeding by means of clamps and sutures. At 8.15 a.m. she was seen by a consultant who estimated the amount of blood in the case room to be at least 2000 c.c. The placenta was mangled; the uterus was well contracted. The blood pressure reading ranged from unobtainable to about 90/50. The patient was given a minimum of anesthesia and the cervix was well exposed by means of Goodwin<sup>9</sup> retractors and a good light. There was no obvious surgical laceration. The bleeding was coming from the posterior lower segment to which pieces of placenta were still adhering. Some of these were removed, but even under direct vision with the retractor in the uterine cavity it was impossible to distinguish between placenta and traumatized uterine wall. Because the patient's condition was precarious, the anesthetist requested that nothing further be done at this time, so the uterine cavity and vagina were tightly packed. By this time five bottles of emergency blood and three bottles of dextran had been given. At 10.30 a.m. bleeding came through the pack. The blood pressure still remained from 90/60 to 50/0. Because no more blood was immediately available, a fourth bottle of dextran was given.

A hysterectomy was started at 12 noon. Efforts were made to control the four main uterine blood supplies as quickly as possible. Blood was run in rapidly into two sites so that 2000 c.c. of blood was given during the operation. The estimated loss during the operation was 1000 c.c. At the beginning of the operation the systolic pressure was 70 mm. Hg and dropped as low as 60 mm. Hg during the operation but by the time the operation was concluded it had risen to 100 mm. Hg. A routine total hysterectomy was performed. The vaginal cuff was oversewn but not closed, to permit drainage from the considerable oozing which occurred.

Immediately after the operation on June 28 the hemoglobin level was estimated at 9.3 g. %. The next day, owing to hemodilution, it was 5.6 g. % in spite

TABLE I.

No.	Author and year of publication	Age	Para	Weeks	Etiological factors	Method of delivery	Treatment	Classification	Pathological findings	Mother	Cause of death	Infant	Remarks		
1	Hink <sup>4</sup>	1896		10		Braxton Hicks	Manual removal	Complete	+	D	Pulmonary	D			
2	Neuman <sup>4</sup>	1896	40	3	40	Man. removal	Manual removal	Complete	+	D	Hemorrhage	L			
3	van Weisse <sup>4</sup>	1897	33	5	36	2 prev. pregs. Man. removal prev. preg.	Braxton Hicks	Vag. hysterectomy	Partial	+	D	Peritonitis	D		
4	Martin <sup>4</sup>	1906	35	3	40	Breech	Manual removal	Complete	+	D	Hemorrhage	D	Pl. previa and diverticulum		
5	Baisch <sup>4</sup>	1907	36	9	40	Man. removal prev. preg.	Vaginal Cesarean sect.	Vag. hysterectomy	Complete	+	L		L	First survivor	
6	Vogt <sup>4</sup>	1917	39	16	40	Breech	Manual removal	Partial	+	D	Hemorrhage				
7	Schmidt <sup>4</sup>	1917	35	5	40	Version	Manual removal	Complete	+	D	Hemorrhage				
8	Schmidt <sup>4</sup>	1917	38	8		Version	Manual removal	Partial	+	D	Peritonitis				
9	Schweitzer <sup>4</sup>	1918	39	15	40	Pl. previa 7 yrs. previously	Man. removal last 3 pregs.	Braxton Hicks	Vag. hysterectomy	Complete	+	D	Hemorrhage	D	Pl. previa and diverticulum
10	Neuman <sup>4</sup>	1923	36	3	38		Cesarean	Abd. hysterectomy	Partial	+	L		L		
11	Neuman <sup>4</sup>	1923	20	3	40		Cesarean	Manual removal	Partial	+	L		L		
12	Bakanow <sup>4</sup>	1928	25	2	40	Endometritis	Cesarean	Abd. hysterectomy	Complete	+	L		L	Spont. rupture of uterus	
13	Klosterman <sup>4</sup>	1929	43	3	40		Breech	Abd. hysterectomy	Complete	+	L		L		
14	Irving and Hurtig <sup>4</sup>	1937	38	9	40	Postpartum hemorrhage twice before	Classical Cesarean sect.	Subtotal hyst., plac. left	Partial	+	L		L	Vesico-abdominal fistula	
15	Wilens <sup>10</sup>	1942		37			Cesarean sect.	Man. removal and packing		L					
16	Jackson <sup>11</sup>	1943	37	2	40	Man. removal followed by sepsis	Cesarean sect.	Supravaginal hyst.	Complete	+	L		L		
17	Shotton and Taylor <sup>12</sup>	1944	28	0	40	Insufflation and D & C	Cesarean sect.	Man. removal and total hyst.			L		L		
18	Riviere and Chastresse <sup>13</sup>	1946					Cesarean sect.	Supravaginal hyst.			L		L		
19	Shannon and Dodenhoff <sup>14</sup>	1947	35	1	42	Man. removal and D & C	Cesarean sect.	Removal by dissection. Packing.	Partial	+	L		L		
20	Gemmell <sup>15</sup>	1947		50			Abd. hysterotomy	Marsupialization	No	L		C	Cesarean sect. 2 yrs. later		
21	Chisholm <sup>16</sup>	1948	35	1	34	Curettage 15 wks. postpartum	Cesarean sect.	Total hyst. 19 days postpart.	Complete	+	L		L		
22	Callender and King <sup>17</sup>	1949	30	1	43	Sepsis following man. removal	Laparotomy	Subtotal with placenta in situ	+	L		D	Spont. rupture of fundus		
23	Kistner, Hurtig and Reid <sup>3</sup>	1951	37	1	39	Prev. lower segm.	Cesarean sect.	Supravaginal hyst.	Partial	+	L				
24	Kistner, Hurtig and Reid <sup>3</sup>	1951	32	1	36	Prev. lower segm.	Cesarean sect.	Supravaginal hyst.	Partial	+	L			Attempted excision of scar	
25	Kistner, Hurtig and Reid <sup>3</sup>	1951	5	2	32	Two previous Cesarean sects.	Cesarean sect.	Supravaginal hyst.	Partial	+	L		D		
26	Kistner, Hurtig and Reid <sup>3</sup>	1951	35	2	37	D & C and 2 prev. Cesarean sects.	Cesarean sect.	Supravaginal hyst.	Partial	+	L		L		
27	Kistner, Hurtig and Reid <sup>3</sup>	1951	27	1	38	Previous Cesarean sect.	Cesarean sect.	Supravaginal hyst.	Partial	+	L		L	Part of placenta left	
28	Kistner, Hurtig and Reid <sup>3</sup>	1951	25	1	34		Cesarean sect.	Supravaginal hyst.	Focal	+	L		L		
29	Kistner, Hurtig and Reid <sup>3</sup>	1951	42	5	32		Classical Cesarean sect.	Supravaginal hyst.	Partial	+	L		D		
30	Kistner, Hurtig and Reid <sup>3</sup>	1951	25	0	40		Vaginal	(Supracervical hyst. 7 days postpartum)	Focal	+	L		L	Succenturiate lobe	
31	Kistner, Hurtig and Reid <sup>3</sup>	1951	37	0	26	5 spont. abortions. Fibroids	Classical Cesarean sect.	Man. removal and packing	+	D	Hemorrhage	D			
32	McKeogh and D'Errico <sup>18</sup>	1951	30	3	31	Two D & C's	Int. podalic version	Manual removal	Partial		L		D	Morbidity in puerperium	
33	Parks, Barter and Hill <sup>19</sup>	1953	31	0	33		Lower segm. Cesarean sect.	Total hysterectomy	+	L		D	Bled several times after 20 weeks		
34	Wright <sup>20</sup>	1954	21	3	37	1 classical Cesarean section and 2 Lower segm. Cesarean sections	Lower segm. Cesarean sect.	Total hysterectomy	+	L		D	Spon. rupt. of clas. scar		
35	Stone, Donnenfeld and Tanz <sup>21</sup>	1954	42	10	42		Cesarean sect.	Subtotal hyst.	+	L					
36	Stone, Donnenfeld and Tanz <sup>21</sup>	1954	33	3	27	Cesarean section	Cesarean sect.	Subtotal hyst.		L					
37	James and Misch <sup>22</sup>	1955	32	1	27	D & C 3 weeks postpartum	Lower segm. Cesarean sect.	Subtotal hyst.	Total	+	L		L	Uterus perforated by finger.	
38	Israel, Siebel and Rubenstein <sup>23</sup>	1955	30	2	39		Lower segm. Cesarean sect.	Total hysterectomy	+	L		L	Bled at 28 weeks.		
39	Chern and Rosenberg <sup>24</sup>	1955	29	2	40	D & C after abort. and 3 wks. post part.	Vaginal	Man. removal Subtotal hyst.	+	L		L	Called low implantation		
40	Wachsman and Moore <sup>25</sup>	1956	29	2			Vaginal	Packed hyst. on 20th day	Partial	+	L		L	App. succenturiate lobe	
41	Wachsman and Moore <sup>25</sup>	1956	25	1	40		Low forceps	Man. removal hyst. 5th day	+	L		L	No evid. for pl. previa		
42	Sedlis, Finn and Loughran <sup>26</sup>	1957	40	12	38	3 Cesarean sects.: 1st for pl. previa	Cesarean sect.	Subtotal hyst.	Partial	+	L		L	Limited to prev. scar	
43	Abitol, Daichman and Mackles <sup>8</sup>	1958	35	2	36	Two previous Cesarean sects.	Lower segm. Cesarean sect.	Total hyst. after 5 hours	Focal	+	D	Toxemia and shock	D	Bled in 7th month	
44	Abitol, Daichman and Mackles <sup>8</sup>	1958	33	0	33		Vaginal	Total hysterectomy	Partial	+	L			Bled from stump after subtotal.	
45	Solomons <sup>27</sup>	1958	35	3	39	D & C's	Cesarean sect.	Total hysterectomy	Total	+	L		L	Percreta and actual rupt.	
46	West and West <sup>28</sup>	1959	37	3	32	D & C after abortion	Lower segm. Cesarean sect.	Total hysterectomy next day	+	L		L	Packing not successful		
47	Millar <sup>7</sup>	1959	42	0	39	D & C 13 years previously	Classical Cesarean sect.	Piecemal removal	Total		D	Hemorrhage	L		
48	Millar <sup>7</sup>	1959	30	7	24		Vaginal Breech		Partial		D	Septicemia and hemor.	D	Died with placenta in.	
49	Millar <sup>7</sup>	1959	42	4	37	Lower segm. Cesarean sect. 3 D & C's following abortions	Lower segm. Cesarean sect.	Hysterectomy	Total		L		L	Placenta membranous, bled 10 weeks.	
50	Foster <sup>29</sup>	1960	40	1	36	Lower segm. Cesarean section	Classical Cesarean sect.	Piecemal removal	Total	+	L		L	Menstruated after 6 mos.	
51	Foster <sup>29</sup>	1960	33	1	33	2 D & C's for menorrhagia	Cesarean sect.	Partial removal	Partial	+	D	Hemorrhage	L	Bled during pregnancy	
52	Friesen	1961	32	3	40	D & C following abortion. Possible previous placenta previa	Vaginal	Total hysterectomy after 6 hours	Total	+	L		L	Bled during pregnancy	

of the administration of a total of 10 bottles of blood. Several more transfusions were given so that before discharge her hemoglobin level had risen to 11.2 g. %. Apart from this, the postoperative course was uneventful. Her temperature never rose above 100° F.

#### Pathology Report

The specimen consisted of a placenta weighing 470 g. and measuring approximately 20 cm. in diameter and 1 cm. in thickness. It was made up of three separate fragments held together by membranous and mutilated tissue. The cotyledons were atrophic at various sites; at others they had been torn away. No hemorrhage or hematomas were noted along the margins of the placenta. The membranes were intact and appeared to be complete.

The cord measured 60 cm. in length and 1 cm. in diameter. The membranes and cord weighed 80 g. Also submitted was a uterus weighing 830 g. and measuring 20 cm. in length and 13 cm. in width at the fundus and 6 cm. in depth. The peritoneal aspect was smooth and was not grossly remarkable. The cervix showed mutilation consistent with manual placental removal. The myometrium measured an average of 2 cm. in thickness and the endometrium showed a yellowish-pink surface in the upper half, whereas in the lower half the surface was shaggy, with numerous depressions and elevated strands of tissue, yellowish-pink in colour, mixed together with blood clot. The endocervical mucosa was not identifiable.

Microscopically, sections of the placenta revealed hyalinization of decidua with early fibrosis of chorionic villi. Examination of the uterus revealed coalescence between chorionic villi and myometrium. The chorionic villi extended focally into interstices of myometrium as interdigitations, the adjacent myometrium presenting marked hyalinization. The adjacent myometrium also contained multinucleated giant muscle fibres. There was minimal attempt at decidua formation. (See Figs. 1 to 3.)

Diagnosis—Placenta accreta.

#### CASES REPORTED IN THE LITERATURE

Table I summarizes in chronological order 52 cases of placenta previa accreta, including the author's case. The first 13 are quoted from Irving and Hurtig,<sup>4</sup> whose excellent article contains all of the original references. Allusions were found in the literature to nine additional cases which seemed to qualify but which could not be verified because the sources were not readily available, usually because they were not in English publications. Cases are being reported more and more frequently. This is probably due mainly to more complete reporting, but if trauma is an etiological factor, as will be suggested, we can expect to see an increasing number of cases of previa accreta because of the increasing popularity of the lower segment Cesarean operation.

#### ETIOLOGY

Basically any factor which interferes with the development of the decidua will tend to produce placenta accreta. Because the decidua of the lower segment is less abundant than that in the fundus,

a placenta implanted in the lower segment is more apt to be abnormally adherent. Table I shows that in the majority of cases the endometrium had suffered some previous trauma, such as that associated with manual removal, curettage, Cesarean section, or sepsis. It is easy to conclude that this trauma interfered with subsequent development of decidua. However, as suggested by Irving and Hurtig<sup>4</sup> in 1937, it is just as probable that earlier manual removals and curettages were necessitated by the same pathological deficiency of decidua that led to the final result. Millar<sup>7</sup> supports this suggestion strongly and believes that the primary decidua deficiency has a hormonal basis. He also minimizes the possible effect of an existing scar, as from a previous Cesarean section. This contention is in contrast to that of Sedlis, Finn and Loughran,<sup>26</sup> who reported a series of 17 collected cases of placenta accreta following a previous section. In 10 of these the pathologically adherent part was limited to the previous scar. If this viewpoint is correct, it could explain the increasing number of cases of placenta previa accreta reported, as being due to the increasing popularity of lower segment Cesarean section.

#### CLINICAL COURSE

In most cases reported the patient was in the latter half of her reproductive life and had had previous pregnancies. In Cases 33, 35, 43, 50, 51 and 52 it was specifically mentioned that bleeding occurred during pregnancy. This was probably due to the position of the placenta; but it might also, by causing fibrosis, be an etiological factor in the later abnormal adherence. Although it is generally considered that placenta accreta produces no symptoms during pregnancy, McKeogh and D'Er-rico<sup>18</sup> believe that occurrence of unusually severe labour-like pains during gestation suggests this condition. The author's patient, in addition to being hospitalized at two and five months because of threatened abortion, was admitted 10 days before term owing to constant lower abdominal pain. The clinical course at term, whether the patient was delivered vaginally or abdominally, did not differ significantly from ordinary cases of placenta previa until attempted removal of the placenta resulted in heavy bleeding.

#### TREATMENT

In 1907 Baisch reported the first patient who survived, having been treated by hysterectomy following (vaginal) Cesarean section. Perusal of Table I indicates that hysterectomy, immediately after diagnosis of the condition during Cesarean section, is by far the safest treatment. More detailed consideration of these cases prompts the generalization that the danger to the patient was directly proportional to the time and effort taken to avoid hysterectomy. Patients delivered vaginally experienced more trouble because more vigorous efforts

at manual removal were made before the condition was recognized and because of the longer time interval between attempted or partial removal and hysterectomy. Packing, as in the author's case, was rarely effective even as a temporary measure.

Subtotal hysterectomy was frequently carried out, although as can be expected this did not always control the bleeding. In Case 14, placental tissue was left attached to the stump and efforts to control the bleeding from this source eventuated in a vesico-abdominal fistula. Abitol, Daichman and Mackles<sup>8</sup> emphasize that, because of involvement of the cervix, the hysterectomy must be total. In one of Abitol's patients a subtotal hysterectomy was performed, followed immediately by removal of the cervical stump, as it appeared that bleeding would not otherwise be controlled.

Granted that hysterectomy is the safest treatment, it is one which is not to be undertaken lightly: so from time to time less radical procedures have been advocated and attempted. Some of these ended disastrously, most of them merely postponed hysterectomy, but a few succeeded. Cases 11, 15, 19, 20, 32 and 50 survived without losing the uterus. Case 50, who had a piecemeal removal at Cesarean operation, began to menstruate six months later, but the only reported pregnancy was in Case 21, reported by Gemmell.<sup>15</sup> In this amazing case hysterotomy was performed 10 weeks after term for removal of a dead fetus, after several medical inductions failed. The placenta, which was found completely adherent over the internal os, was left in place and the uterine cavity was marsupialized by suturing the edges of the uterine incision to the fascia. Two years later this patient was delivered again, by Cesarean section. In Case 24 an attempt was made at the time of Cesarean operation to excise the scar of a previous section to which the placenta was densely adherent. Excessive hemorrhage made this too dangerous and hysterectomy had to be carried out. McKeogh and D'Errico,<sup>18</sup> who reported Case 32 in a series of 11 cases of placenta accreta, make a very strong plea for conservatism.

#### COMPLICATIONS

The complication encountered most frequently was rupture of the uterus. This was spontaneous in Cases 12, 22, 34 and 45; in Case 37 the uterus was perforated by the surgeon's finger. Infection was mentioned several times and was specifically included in the cause of death in Cases 3, 5 and 48. Pulmonary embolism was considered the cause of death in Case 1. The vesico-abdominal fistula of Case 14 has already been mentioned. Uterine inversion, a rather common complication of placenta accreta in the fundus, did not occur when the accretic placenta was in the lower segment.

#### MORBIDITY AND MORTALITY

Of the 52 cases reported, 13 (25%) ended fatally. It is noteworthy that four of these were reported

in the last three years and seem to be a direct accompaniment of a trend to more conservative management. For comparison, of 36 patients treated by hysterectomy, three (8.5%) died; whereas of 16 cases in which the uterus was conserved, 10 (62.5%) ended fatally.

#### DISCUSSION AND CONCLUSIONS

In the past, combined placenta previa and accreta has been rare enough that most obstetricians never encountered such a case in a life-time of practice. If it is true, as seems altogether likely, that a uterine scar favours the occurrence of abnormal adherence of the placenta, then the increasing frequency of lower segment Cesarean sections may be expected to result in more frequent occurrence of this combination.

In the individual obstetric patient there is little that might lead the doctor to suspect the existence of an abnormally adherent placenta until difficulty is encountered in its removal. The possibility should be considered when there is a history of previous trauma to the uterus, such as previous section or myomectomy, curettage, and postabortal or postpartum sepsis, and especially a previous manual removal of an adherent placenta. Unusual pain in pregnancy is met with frequently enough that it probably has no significance in this regard.

After the strain of safely delivering a patient with placenta previa, most obstetricians would prefer to treat an unexpected accompanying placenta accreta in the quickest and simplest manner, that is, by immediate hysterectomy. On the basis of reported experience this is also the safest treatment. However, no one man would have acquired sufficient experience to make the diagnosis with certainty. Parks, Barter and Hill<sup>19</sup> emphasize this point; they report that of 10 patients who underwent hysterectomy the provisional diagnosis of placenta accreta could not be confirmed by pathological study in six. Furthermore, since some patients have been treated successfully without sacrifice of their reproductive function and have had at least one subsequent pregnancy, it is worth considering the conditions under which conservative management might be considered and the precautions to be taken to ensure the patient's safety.

In several of the patients in whom the placenta was left *in situ*, including the one subjected to marsupialization, the authors commented that it was not expelled later, either piecemeal or by copious discharge of autolyzed products. Apparently the natural history of this condition eventuates in placental absorption as in the case of an abdominal pregnancy. This suggests that in the absence of decidua a placenta should be treated the same way whether it be intra- or extra-uterine. There are, however, three outstanding differences, depending on the location. If the placenta is extrauterine, it is safe to assume that there is practically no decidua; that is, that the condition is comparable to a total placenta accreta. In the uterus

it is quite likely that part of the placenta is implanted on relatively normal decidua (partial accreta) and spontaneous separation of this part will almost certainly lead to intractable hemorrhage. Secondly, in the case of the extrauterine placenta it is much less likely that ill-advised attempts will be made to remove it because one expects this to be a dangerous procedure. The third difference, unlike the first two, favours the patient with the intrauterine placenta. If profuse hemorrhage does occur, usually as a result of partial separation, this bleeding can be stopped at its source relatively easily by ligating four sets of vessels and removing the uterus. In the extrauterine pregnancy a similar procedure might involve multiple bowel resections or might be completely impossible.

In most cases the amount of hemorrhage as a result of partial spontaneous separation or ill-advised manual removal will make emergency hysterectomy mandatory. In these the decision is obvious. In cases of total placenta accreta recognized as such before heavy bleeding is produced, the further management depends on such factors as the patient's age and desire for more children and on whether the condition becomes apparent after vaginal or abdominal delivery.

If, on attempted manual removal after vaginal delivery, no line of cleavage can be found, it would seem advisable to postpone strenuous efforts until arrangements have been made to proceed with emergency hysterectomy should this become necessary. If partial separation, as evidenced by hemorrhage, does not occur, no further efforts are necessary. With antibiotics to combat infection and prompt transfusion and hysterectomy in reserve in cases of hemorrhage, these patients can quite safely be followed expectantly.

If the accretic placenta is found during abdominal delivery, reproductive function of the patient can best be preserved by restraining the temptation to remove the placenta by whatever methods seem to be necessary. Experience has shown that dissection or piecemeal removal almost inevitably terminates in hysterectomy. If bleeding does not occur, serious consideration should be given to leaving the placenta *in situ*, as the patient's desire for more children might be strong enough to warrant the calculated risk of another laparotomy for emergency hysterectomy. Obviously such a course would not be warranted if the patient's permission for tubal ligation had already been obtained.

#### SUMMARY

The subject of accretic placenta previa is reviewed and the case history of a patient with this disorder is described.

Fifty-two such case reports in the literature are summarized and analyzed.

The similarity to extrauterine pregnancy is pointed out and a plea is made for conservative treatment in selected cases. The safeguards necessary for such management are described.

I wish to acknowledge my gratitude to: Dr. M. E. Burke for the opportunity of sharing in the care of this patient and for permission to report the case; Dr. F. H. Burgoyne and Dr. M. Hamonic of the Department of Pathology, St. Boniface Hospital, for their encouragement and assistance; Mr. Lloyd Stanford of the Department of Photography for the pictures used in the illustrations; and Mrs. Margaret Whitenect, Secretary of the Perinatal Mortality Study Committee, for assistance in preparation of the manuscript.

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#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO TYPHOID IN THE WINNIPEG GENERAL HOSPITAL

During the years 1901-10 seventy-one cases of typhoid fever have developed amongst members of the house staff, nurses, physicians, orderlies, etc., of the Winnipeg General Hospital. The distribution of the cases and certain other facts in relation to them are shown in the following chart:

	1901	'02	'03	'04	'05	'06	'07	'08	'09	'10	Total	Died	Days in hospital
Nurses.....	2	5	5	4	5	10	5	3	2	7	48	2	2333
Male help.....				3		3	1	1	1	1	10	3	408
Maids.....						2	4		1		7	1	504
Physicians.....	1		1				4				6	1	178
	3	5	6	7	5	15	14	4	4	8	71	7	3523

In none of these cases was there any trace of a house epidemic except in 1907. In that year no less than nine—three nurses, two maids and four physicians—were taken sick with typhoid between the dates August 18 and August 29. The cause of this epidemic has never with certainty become known, but it is very likely that it was due to the infection of a single ten gallon can of milk contaminated by flies.—S. J. S. Peirce, *Canadian Medical Association Journal*, 1: 503, June 1911.

## CASE REPORT

CARCINOMA OF THE STOMACH  
WITH MYELOSCLEROSIS:  
PRESENTATION OF A CASE AND  
REVIEW OF THE LITERATURE

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SMALL carcinomas of the stomach may remain undiagnosed during life. Not infrequently, even at postmortem examination the primary lesion may be missed.

These patients may present with evidence of disease of the lung or bone marrow which is later shown to be due to metastatic carcinoma from an unknown primary site. While rare, some 25 cases of this type have been reported in the world literature in the past 25 years since Jarcho's<sup>1</sup> original review.

The following is a report of a patient who had a severe anemia and the signs and symptoms of myelosclerosis which was shown to be due to widespread metastatic carcinoma from a microscopic primary tumour in the stomach.

J.H., a 37-year-old male taxi driver, was admitted to the Queen Mary Veterans Hospital on February 1, 1959. He had been in excellent health until the first week in January 1959, at which time he noted the onset of weakness, pallor, abdominal pains, dyspnea and cough productive at first of whitish and later of blood-tinged sputum.

He was admitted to another hospital on January 12, 1959, where a diagnosis of acute bronchitis was made. During this admission, his hemoglobin value was 78%, the leukocyte count was 7200 per c.mm. with a normal differential count and his chest radiograph showed scattered fine infiltrations with vascular congestion. He was treated with penicillin and streptomycin and was discharged from hospital on January 20, 1959.

After discharge from hospital, his original symptoms persisted and increased. Epistaxis developed together with "foggy vision" and a 10 lb. weight loss. Because of these disturbing symptoms, he was admitted to the Queen Mary Veterans Hospital.

Physical examination on admission revealed a pale, ill male who coughed frequently. His blood pressure was 130/75 mm. Hg, pulse rate was 108/minute and the respiratory rate 28/minute. A few small, firm lymph nodes were palpable in the neck, axilla and inguinal region. A few "bruised" areas were noted over both legs. The thyroid was not palpable. The sternum was tender to pressure. Both lung bases were dull to percussion with decreased air entry at the right base.

A few crepitant rales were heard at both lung bases. The heart sounds were normal. The liver was percussed four finger-breadths below the right costal margin and was tender to palpation, although the edge could not be felt. The splenic tip was questionably palpable. The kidneys could not be felt. Rectal examination was negative and the prostate was not enlarged. The optic fundi showed numerous flame-shaped hemorrhages and bilateral well-defined whitish infiltrates radiating from the discs.

Laboratory findings on February 2 were as follows: blood urea nitrogen 11.3 mg. %, sodium 128 mEq./l., potassium 4.3 mEq./l., total protein 5.26 g. %, calcium 8.8 mg. %, phosphorus 3.36 mg. %, alkaline phosphatase 150 Shinowara units, acid phosphatase 0.47 Shinowara units, serum uric acid 6.2 mg. %, and liver flocculation tests were negative. One 24-hour specimen of urine contained 29 mg. of calcium. The urinalysis was normal. His hemoglobin value was 5.2 g. %, hematocrit 15%, leukocyte count 6450/c.mm., platelet count 86,000/c.mm., mean corpuscular volume 84  $\mu^3$ , mean corpuscular hemoglobin 29  $\mu\text{g.}$ , mean corpuscular hemoglobin concentration 35%, prothrombin time 16 sec., control 13 sec., bleeding time 7 min. 30 sec., clotting time 6 min. A Rumpel-Leede test was weakly positive. The direct Coombs test was negative. The differential leukocyte count showed 33% mature and 9% young neutrophils, 8% myelocytes and metamyelocytes, 45% lymphocytes, 3% monocytes, 2% eosinophils and 1 basophil. There were 9.2% reticulocytes and 15% normoblasts. On the blood film, the red blood cells showed anisocytosis, poikilocytosis and polychromatophilia.

Sputum cultures were all negative for pathogenic bacteria and malignant cells. His chest radiograph (Fig. 1) revealed a small pleural effusion with exaggerated bronchovascular markings, most marked at the left base. Radiographs of the dorsal and lumbar spine (Fig. 2) demonstrated a marked increase in bone density. The long bones were normal. Skull roentgenograms showed normal bone density with scattered areas of increased translucence. Five attempts at sternal puncture and one iliac crest puncture produced only small amounts of blood. The bony cortex was thick and resisted penetration.

The rapidity of development of leuko-erythroblastic anemia and the lack of a very large spleen favoured the diagnosis of metastatic carcinoma of the bone marrow, rather than a diagnosis of myelosclerosis. An attempt was made to locate the primary tumour.

The patient was transfused with five units of whole blood between February 3 and 5, 1959, and prednisone 40 mg. daily was started on February 5. His hemoglobin level rose to 10.2 g. % on February 7, but the platelet count remained at 72,000/c.mm. The leukocyte and differential counts remained unchanged.

On February 7, the patient awoke with pain behind the right eye. This persisted, became severe and was associated with vomiting and restlessness. Funduscopic examination revealed the presence of a new retinal hemorrhage but the disc margins were still well defined. He soon lapsed into coma, with Cheyne-Stokes breathing, inequality of the pupils, papilledema and seizures. He died on February 8, 1959.

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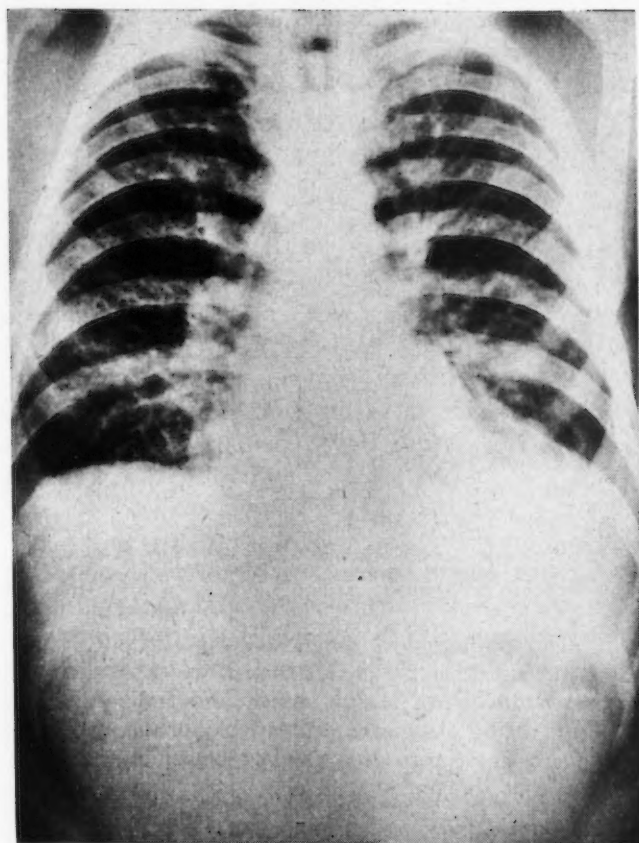


Fig. 1.—Increased bronchovascular markings. Slight effusion left base.

At autopsy, blood-tinged fluid was found in the pericardial and pleural cavities. The heart was normal except for the presence of a number of petechiae over the pericardial surface. The lungs were slightly firmer than usual, with some congestion and edema of the lower lobes. The peribronchial and mediastinal lymph nodes were slightly enlarged, although grossly normal in appearance. Several discrete, firm lymph nodes were noted in both axillae, inguinal regions and the mesentery of the small intestine. The stomach showed slightly hypertrophied rugae over the greater curvature with two small erosions on the posterior wall in the body of the stomach. In the adjacent greater omentum, two small nodes were found. The remainder of the intestinal tract, the kidneys, prostate and thyroid were normal. The liver and spleen were both enlarged although normal in appearance. A fresh hematoma was present in the right occipital lobe of the brain which had ruptured into the ventricular system.

Microscopic examination of the lungs (Fig. 3) revealed extensive involvement of perivascular and peribronchiolar lymphatics with carcinoma cells. These were arranged in cords and showed acinar formation in some areas. Similar malignant cells were found in the bone marrow and lymph nodes. The bone marrow also showed extensive replacement of hematopoietic elements by dense fibrous tissue in which clusters of malignant cells were embedded. The bony trabeculae were somewhat thinned and eroded (Fig. 4). The liver and spleen showed evidence of extramedullary hematopoiesis. Routine sections of other organs were normal.

In an attempt to localize the site of the primary tumour new sections were prepared from the stomach through the areas of the small erosions (Fig. 5). Each of these sections revealed a sharply demarcated malignant change (Fig. 6) in the mucosa which had not involved the submucosa. This change was characterized

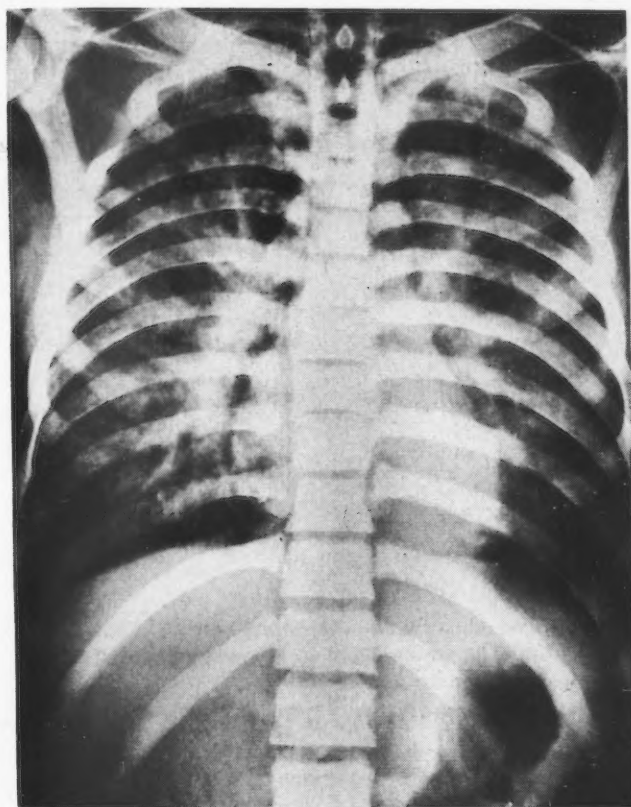


Fig. 2a.—Dorsal spine. Note marked density of bones.

by an abrupt loss of architecture with almost complete absence of glandular elements. The carcinoma cells were large, pleomorphic, deep-staining anaplastic cells with large nuclei. Some cells presented a signet-ring



Fig. 2b.—Lumbar spine. Note marked density of bones.

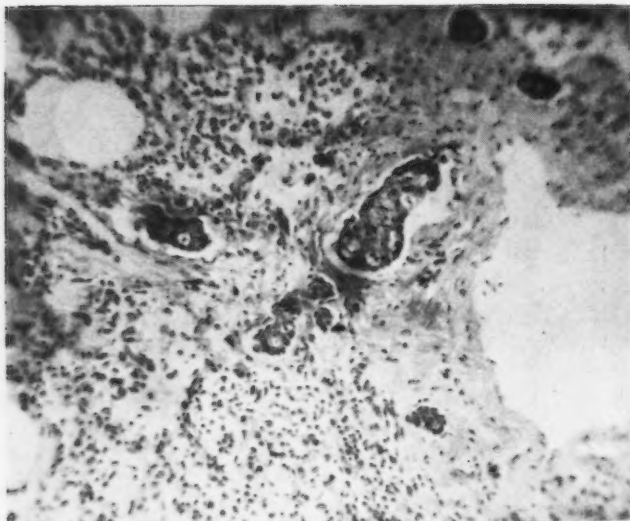


Fig. 3.—Peribronchiolar lymphatics with tumour cell emboli.

appearance. A few anaplastic cells could be seen penetrating the inner layer of the muscularis mucosae. The submucosa underlying the carcinoma was markedly thickened by fibrosis, although this change was not

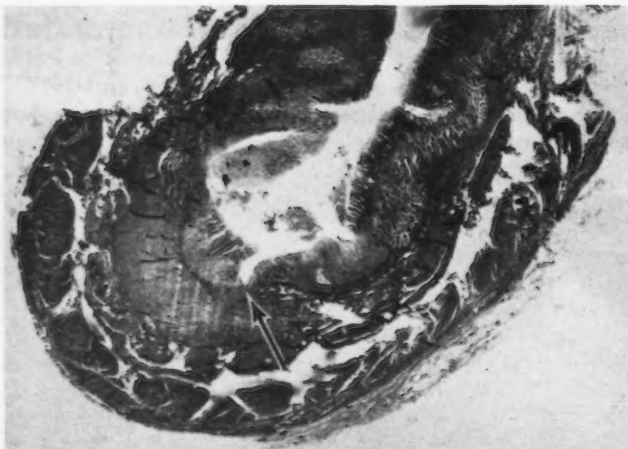


Fig. 5.—Section of gastric tissue,  $\times 50$ . Note small erosion in the base of the villi.

seen elsewhere in the stomach. Periodic-acid Schiff and mucicarmine stains of the stomach, bone marrow and lungs were positive for mucin in most of the neoplastic

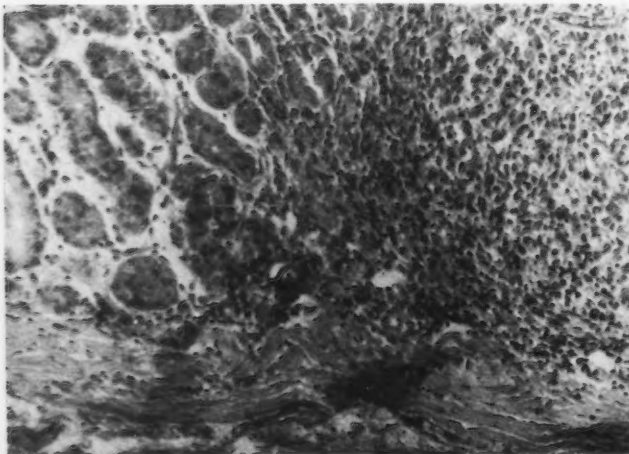


Fig. 6a.—Low-power view showing transition area between normal gastric mucosa and tumour tissue.

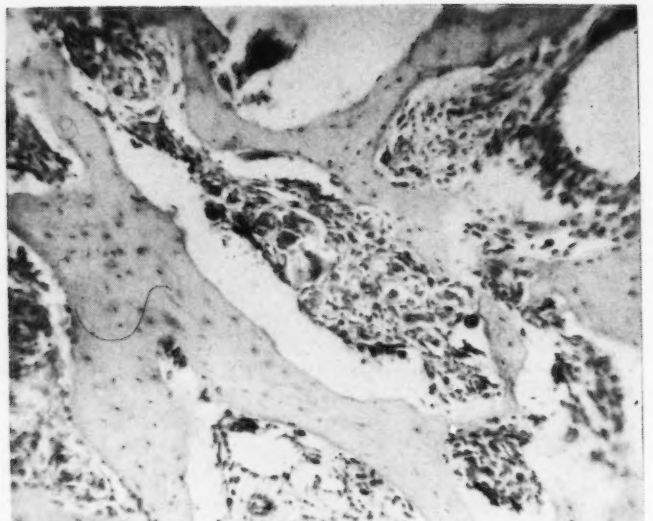


Fig. 4.—Section of vertebral bone showing invasion by tumour cells, marked fibrous tissue reaction, and some thinning of bony trabeculae.

cells. The pathological diagnosis was: Primary small adenocarcinoma of the stomach with widespread carcinomatosis involving lymph nodes and bone marrow, the latter being associated with myelofibrosis and myelosclerosis. There was also extensive lymphangitic carcinomatosis of the lungs.

#### DISCUSSION

The association between gastric carcinoma, lymphangitic carcinomatosis of the lungs and extensive bone marrow metastasis was well summarized by Jarcho<sup>1</sup> in 1936. Since then, a number of reports have appeared sporadically in the literature.<sup>2-14</sup> The similarity between these cases both anatomically and clinically as first noted by Jarcho has been borne out in subsequent reports and can be summarized as follows:

1. The condition usually occurs in young adults under 40 years of age.
2. The clinical course is usually brief and fulminant.
3. The primary gastric carcinoma is most often small and asymptomatic. It may escape radiographic detection and may at times not be visible in the gross pathological specimen.

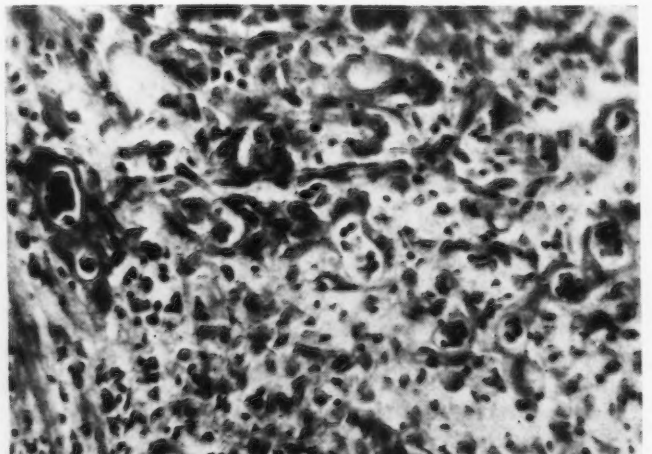


Fig. 6b.—High-power view of gastric tumour showing signet cells.

4. Microscopically the primary tumour is usually of the scirrhous or "diffusely infiltrative type".<sup>1</sup>

5. Pulmonary metastases are often visible only on microscopic examination and involve lymphatic spaces (perivascular, peribronchial and subpleural) and occasionally pulmonary blood vessels in what has been called lymphangitic carcinomatosis.

6. Symptoms associated with pulmonary metastasis are dyspnea, cyanosis and non-productive cough. Radiographs of the lungs are characteristic and exhibit thin stringy lines in the lung fields which branch out from the hilum.<sup>6</sup>

7. Bone marrow metastases tend to be widespread, with extensive replacement of hematopoietic elements by fibrous tissue as well as tumour cells.

8. Clinical findings associated with bone marrow metastases are those of myelophthisis and extramedullary hematopoiesis. Purpura associated with thrombocytopenia, anemia of varying severity, normoblasts, reticulocytes and immature white blood cells are found and are usually very prominent.

9. Hepatosplenomegaly associated with myeloid metaplasia, and occasionally metastatic lesions, is frequent.

10. The presenting symptoms are due to bone marrow or pulmonary metastases, depending on which organ is more affected.

11. Occasionally, the ovaries are involved with the development of Krukenberg tumours.

The patient described in this report presents a classical illustration of this condition. The minute nature of the primary lesion bears emphasis. Lesions of this type may be easily overlooked and may explain similar cases described in the literature where no primary tumour was detected.<sup>22</sup> Signs and symptoms referable to the widespread tumour metastasis to bone marrow and lung were the outstanding features of this patient. The bone marrow metastases were the more prominent and in a very short time led to his death.

The blood picture in this case was similar to that seen in leuko-erythroblastic anemia; it was characterized by the presence in the circulating blood of immature leukocytes and nucleated red blood cells, the latter usually in large numbers.<sup>16</sup> This picture may be seen in a number of different conditions which give rise to space-occupying lesions of the bone marrow. These include carcinomatosis of the bone marrow from any source, Hodgkin's disease, myelomatosis, myelofibrosis and myelosclerosis of unknown etiology, osteopetrosis and primary xanthomatosis.<sup>8, 16</sup>

Leuko-erythroblastic anemia is usually normocytic in type, with the presence of many circulating nucleated red blood cells, mainly normoblasts; reticulocytosis, polychromatophilia and poikilocytosis are also noted. The leukocyte count may be normal, decreased or increased, although the latter is unusual in patients with carcinomatosis. Variable

numbers of myelocytes and, occasionally, myeloblasts are present. The platelet count is normal or decreased.<sup>16</sup>

Several theories have been advanced to explain the development of anemia in cases of widespread carcinomatous metastases to bone marrow.<sup>4, 8, 16, 17</sup>

(a) Crowding out of the hematopoietic elements in the bone marrow by the tumour tissue is considered by some to result in the anemia in such cases. This theory cannot explain the anemia in all patients, since, as pointed out by Vaughan,<sup>18</sup> the space taken up by the tumour may be relatively small while the rest of the hematopoietic system undergoes hyperplasia.

(b) Hemolytic anemia with shortened red blood cell survival is important in many patients, especially those in whom red blood cell production is insufficient to keep pace with the increased cell breakdown. The cause of hemolysis has not been explained in the majority of cases. A positive Coombs test was noted in two of the cases reported in the literature<sup>4, 8</sup> associated with gastric carcinomatosis, although in one this test was only weakly positive and was negative on repeat examination.

(c) Blood loss via the gastrointestinal tract can be expected in a certain proportion of patients with gastric carcinoma and again with inadequate regenerative bone marrow response. Varying proportions of these three factors are probably important in different cases.

The following theories have been suggested to explain the bizarre blood picture noted in cases of leuko-erythroblastic anemia due to carcinomatosis.

(a) Immature circulating erythrocytes and leukocytes are not uncommonly associated with hemolytic anemia due to any cause, although not usually to the degree seen here.

(b) A direct effect of the tumour tissue on adjacent marrow has been proposed by some<sup>17-19</sup> whereby the fine control system of the bone marrow is lost and immature cells are released into the circulation. Whether this effect is mediated by direct irritation,<sup>19</sup> local nutritional deficiency,<sup>18</sup> a metabolite of the tumour cells<sup>19</sup> or some other factor is at present unknown.

(c) Areas of myeloid metaplasia in liver, spleen and elsewhere also lack the fine regulatory mechanism characteristic of the normal bone marrow, and may also add immature blood cells to the circulation.

The presence of clotting defects is often very prominent, as noted by Jarcho<sup>1</sup> and others.<sup>3, 10, 14</sup> Hemorrhage and purpura are associated with thrombocytopenia, although in one case<sup>3</sup> a decrease in prothrombin complex and fibrinogen was also noted. In view of these defects in clotting, it is not surprising that a certain percentage of cases die from cerebral hemorrhage, as did the patient described in this report.

Generalized homogeneous increase in bone density is uncommonly seen radiologically. It occurs in some cases of carcinomatosis with osteoblastic metastasis to the bone, the prostate being the usual primary site. Idiopathic myelosclerosis, osteopetrosis, Paget's disease and fluorine poisoning are other conditions associated with this radiologic appearance. Osteosclerosis was noted during life in two of the reported cases of gastric carcinoma,<sup>4, 12</sup> and in one other probable case.<sup>22</sup> The characteristic pathological picture is one of thickened bone trabeculae with no distortion of architecture. The marrow space may be diminished in places, with an increased content of fibrous tissue. It is usually assumed that myelosclerosis in these cases is due to the presence of carcinoma tissue in the bone marrow, although humoral factors cannot be ruled out. Why one tumour should cause osteoblastic lesions and another osteolytic changes is unknown, but the mechanism of such changes probably involves the osteoblasts and osteoclasts of bone. Alkaline phosphatase is secreted by the osteoblasts and in some unknown way aids in new bone formation. In the absence of liver disease the level of alkaline phosphatase in the serum is a reflection of osteoblastic activity. Therefore cases of carcinoma, metastatic to bone, which have predominantly osteoblastic metastases, are associated with more marked alkaline phosphatase elevations in the serum as compared to those with metastases causing osteolytic lesions.<sup>15</sup> In two of the reported cases, alkaline phosphatase levels of 20 and 28 King-Armstrong units were described.<sup>4, 8</sup> The markedly elevated alkaline phosphatase associated with osteosclerosis as noted in our patient is unique and is of the order of magnitude previously reported in some cases of Paget's disease, hyperparathyroidism and metastatic prostatic carcinoma.<sup>15</sup> There was no evidence in this case that hepatic factors contributed to the very high level of this enzyme.

Lymphangitic carcinomatosis of the lungs is most frequently associated with a primary lesion in the stomach,<sup>1</sup> though other primary sites have been recorded.<sup>1, 6</sup> Lymphatic spread to the lung is said to be via the perigastric, tracheal and mediastinal lymph nodes.<sup>20</sup> The malignant cells then spread in a retrograde fashion from the hilus to the pleura, producing the characteristic pathological and radiological picture.

Retinal changes consisting of white-centred hemorrhages have been described by Brust<sup>21</sup> as occurring in cases of severe anemia. These also occur in leukemia, and Brust postulates that the hemorrhages correlate better with the fall in hemoglobin than with the degree of thrombocytopenia. In view of this interesting observation one might speculate that the marked retinopathy in this case was largely due to the severe anemia.

The widespread, diffuse nature of the metastases from this small gastric carcinoma bears emphasis. This makes early diagnosis of the primary lesion almost impossible; even late in the course of the

illness it may be very difficult. Numerous blood transfusions will be required by many of those patients who survive for an appreciable length of time, particularly if there is hemolysis or blood loss. Prednisone was administered to this patient in an attempt to elevate his platelet count. Despite this, thrombocytopenia continued and was probably responsible for the cerebral hemorrhage which resulted in his death.

#### SUMMARY

The occurrence of a minute asymptomatic carcinoma of the stomach in a young male is reported. His illness ran a fulminant course with extensive metastases to the lung, lymphatics and bone marrow, resulting in severe myelosclerosis with extramedullary hematopoiesis and leuko-erythroblastic anemia. A unique feature in this case was the presence of a markedly elevated alkaline phosphatase with widespread osteosclerosis of the dorsal and lumbar spine.

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#### PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Dr. J. Friedjung, of Vienna, recently tabulated his observations upon one hundred only children. Their ages varied from two to ten years. Eighteen suffered from severe nervous disorders, and sixty-nine were slightly neuropathic. Of the hundred only children, none of them more than ten years old, eighty-seven were in an abnormal nervous condition. Among a hundred children in families of more than one child, but thirty-seven cases of nervous trouble could be found. The nervous defects in the only children seemed to have reacted unfavourably on their physical condition. An unusually large number were found to be sufferers from poor appetites, indigestion, intestinal troubles, and general malnutrition.—*Canadian Medical Association Journal*, 1: 508, June 1911.

## SHORT COMMUNICATION

### A COMPARATIVE CLINICAL STUDY OF THREE HYPNOTIC DRUGS\*

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IN A PRELIMINARY STUDY on the sleep-inducing and sleep-sustaining characteristics of pentobarbital sodium (Nembutal) 100 mg., butabarbital 50 mg. and meprobamate 200 mg. (Neo HS†), and thalidomide 100 mg. (Kavedon)‡<sup>1,2</sup> the findings had suggested that pentobarbital was the most effective and thalidomide the least effective in the doses chosen for this experiment.

#### METHOD AND PROCEDURE

The trial was repeated in a controlled single-blind five-day experiment. The preliminary uncontrolled study had extended over a period of 20 days.

Twenty patients on an open ward of a mental hospital were selected for this clinical trial. The criteria for selection of the sample group were willingness to co-operate in the experiment and the fact that the patients were not receiving any other medication. The patients were placed in four separate bedrooms each containing five beds, and their daily routine was modified in the following manner. No patient was permitted to be in the room or to sleep during day time, but at 8.50 p.m. they were asked to go to bed. At 9 p.m. the medication was given without comment and thereafter a check was made every 15 minutes to ascertain who was sleeping. A patient was judged to be asleep if he did not turn or move when a flashlight was focused on him. The time elapsed from the time of administration of the medication until the patient fell asleep was measured, as well as the frequency with which he got up during the night. The time when patients awoke in the morning was registered and their level of activity during the morning hours was rated. For this purpose a 0 to 3 rating scale was devised in which the rating 0 indicated that the patient remained in bed after awakening and the rating 3 indicated that he engaged in his normal activities.

The experiment lasted five days. On the first day 100 mg. pentobarbital (one capsule of Nembutal), on the second day one placebo tablet, on the third day 100 mg. butabarbital and 400 mg. meprobamate (two tablets of Neo HS), a semi-barbiturate, on the fourth day two placebo tablets and on the fifth day 100 mg. thalidomide (two tablets of Kavedon), a non-barbituric hypnotic, were administered.

\*From the Verdun Protestant Hospital, Verdun, Que.

†Neo HS was generously provided by Neo-Drug Company.

‡Kavedon was generously provided by the Wm. S. Merrell Company.

#### RESULTS

Results are presented in Table I.

TABLE I.—MEANS OF THE SLEEP-INDUCING AND SLEEP-SUSTAINING CHARACTERISTICS OF THE ADMINISTERED COMPOUNDS

Drug	Onset of sleep (in minutes)	Number of times up at night	Duration of sleep (in minutes)	Morning activity
Pentobarbital 100 mg. (one capsule of Nembutal)	42	0.85	538	2.85
Placebo one tablet	67	1.35	501	2.70
Butabarbital 100 mg. and meprobamate 400 mg. (two tablets of Neo HS)	51	1.10	528	2.85
Placebo two tablets	63	1.40	518	2.85
Thalidomide 100 mg. (two tablets of Kavedon)	58	1.20	522	2.75

#### DISCUSSION

The mean results as illustrated in the table suggest that, of the three drugs tested, pentobarbital sodium in the dosage chosen has the strongest hypnotic efficacy. Subjects fell asleep faster, got up on fewer occasions during the night and slept longer than on any other compounds. It should be noted that two Neo HS tablets contain quantitatively the same amount of barbiturate as one Nembutal capsule and that Neo HS, in addition, contains meprobamate. Thalidomide (Kavedon) appeared to be the least effective at the dosage chosen for this study, though it was still more active than both placebos.

Three of the 20 subjects complained of "hang-over" the morning after administration of thalidomide.

Placebo administration in both dosages produced distinctly inferior effects when compared with the three active drugs investigated.

#### SUMMARY

The effects of three sleep-inducing compounds were compared with each other and with a placebo in a clinical experiment. Pentobarbital sodium (100 mg.) appeared to have the most pronounced and thalidomide (100 mg.) the least pronounced hypnotic characteristics as judged by the behavioural parameters which were assessed.

We are indebted to Dr. H. E. Lehmann for his criticisms and assistance in the preparation of this paper.

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THE CANADIAN MEDICAL ASSOCIATION  
**JOURNAL**  
LE JOURNAL DE  
L'ASSOCIATION MÉDICALE CANADIENNE

*published weekly by*

THE CANADIAN MEDICAL ASSOCIATION

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#### VOCATIONAL REHABILITATION OF THE DISABLED

**F**EW practising physicians would disagree with the observation that "... under present provisions, securing the various services necessary to the vocational rehabilitation of the disabled can be a baffling and time-consuming process" as stated recently by the Honourable Michael J. Starr, Canada's Minister of Labour.<sup>1</sup> While this is hardly so in the case of disabled veterans, industrial accident victims and a few other categories of physically handicapped persons, doctors are frequently confronted by the problems of disabled people for whom there seems to be no authority responsible for providing the comprehensive medical, social and vocational rehabilitation services which they need. The importance of solving this problem has been discussed previously in the editorial pages of this journal.<sup>2</sup>

Mr. Starr's comment was made during the House of Commons Debate on Bill C.84, the new Vocational Rehabilitation of Disabled Persons Act. This measure appears designed to correct the situation, at least in so far as this lies within the competence of Parliament.

The Act authorizes the Minister to make agreements to pay 50% of the costs incurred by any Province in providing a comprehensive program for the vocational rehabilitation of disabled persons. Earlier measures, such as the Medical Rehabilitation Grant, placed ceilings on the Federal Government's financial participation in rehabilitation programs. These restrictions tended to discourage action by Provincial Governments. The new Act sweeps these impediments aside.

The Act will not, by its mere existence, automatically achieve the Federal Government's high purposes. It places the onus squarely on the Provinces to determine what comprises a comprehensive program for the vocational rehabilitation

of disabled persons. Ultimate success in this endeavour will depend largely upon the initiative, vision and vigour displayed by the Provinces, but it may be hoped that the Federal Government will decline to make agreements with Provinces proposing anything less than the comprehensive program which the Act calls for.

The Act provides that a comprehensive program of vocational rehabilitation may include "services and processes of restoration", and that its objective is to enable disabled persons to become capable of pursuing regularly "a substantially gainful occupation". Should a narrow construction be placed on either of these terms, there is danger that essential medical and surgical procedures may not be included, and that housewives and others, whose rehabilitation objectives do not embrace remunerated employment, may be excluded from assistance.

The complex problems presented by the disabled rarely conform to the neat functional distribution of responsibilities among government departments. The baffling process which Mr. Starr refers to is likely to be perpetuated at the provincial level unless responsibility for each provincial rehabilitation program is concentrated in the hands of one Minister and one department. This is necessary for effective leadership and improved co-ordination of the related activities of other government departments and voluntary agencies. A study of the system whereby the Department of Veterans Affairs assumed total responsibility for the rehabilitation of disabled veterans and yet achieved a high degree of participation by other governmental and voluntary agencies should prove illuminating for those responsible for planning the expanding rehabilitation programs envisaged under the new Act.

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#### CANADIAN FRIENDS OF THE LONDON POSTGRADUATE MEDICAL SCHOOL

**E**STABLISHED in 1931 under Royal Charter and opened in 1935 by King George V, the Postgraduate Medical School of London, England, is unique among the institutions of its kind in the British Commonwealth. Today, under the presidency of Field Marshal The Right Honourable Earl Alexander of Tunis, former Governor General of Canada, the School has become one of the world's outstanding medical centres, specializing in postgraduate medical education in various branches of medicine, surgery and pathology. In these fields it has provided facilities for specialist training and advanced postgraduate study to more than 14,000 doctors from every sector of the world. One-tenth of those who have pursued their postgraduate studies and training at the School are Canadians.

The calibre of these 1400 alumni now engaged in the application of their professional skills in Canada bears testimony to the contribution that the London Postgraduate School has made to Canadian medicine.

Opportunities for postgraduate training abound in many centres throughout Canada, and in certain fields of medicine the quality of such training compares favourably with that available anywhere on earth. Nevertheless, a 20th century Mecca such as the London Postgraduate School offers that unique and indefinable broadening of experience and viewpoint that can only be acquired through day-to-day association with the keen, inquiring and penetrating young intellects that congregate there from every quarter of the globe.

Canadians can continue to share in the benefits of the Postgraduate Medical School only if sufficient numbers of Canadian doctors continue to study there. To provide financial assistance through bursaries not presently available to students from Canada, and to assist the School in acquiring additional facilities necessary for the continuation of its work, an appeal is being conducted to raise one million dollars in Canada. During the past two years an association known as the *Canadian Friends of the Postgraduate Medical School of London, England*, has been organized to foster and maintain contacts between Canadian doctors and the School, recognizing that it is playing a most important role in raising the level of medical practice throughout the world and in strengthening Commonwealth relationships. This organization, which is sponsored by prominent members of the medical profession and by some of the most outstanding leaders of Canadian business and industry, is presently engaged in its fund-raising campaign in support of a cause that justly merits the support and encouragement of Canada's medical profession.

#### STUDIES ON CHILDHOOD MALIGNANCIES AND CONGENITALLY DETERMINED LEUKEMIA

A RECENTLY reported study of leukemia and other malignant diseases of childhood presents an interesting working hypothesis and discusses some of its epidemiologic implications (Stewart, A., *Brit. M. J.*, 1: 452, 1961). These observations are based on examination of the records of 1638 children who died from either leukemia (780) or cancer (858), and those of 1638 living children. Special note was made of the relationship between leukemia and such other conditions as pyogenic infections, mongolism, family history of malignant disease and prenatal x-ray exposure.

Apart from rubella, none of the infectious diseases were recorded more often by cases than by controls, but the more serious illnesses such as pneumonia, acute bronchitis, other serious pyogenic infections, burns and fractures, were reported, collectively and separately, more often in children

who subsequently died of leukemia. The commonest major defect which occurred in association with leukemia was mongolism. The survey records, which included data about relatives, confirmed the existence of leukemia and lymphadenoma "fraternities". They also indicated that children who were exposed to x-rays early in the mother's pregnancy were more likely to develop cancer than leukemia, and that the risk of both diseases was far greater than the risk attached to the taking of x-rays shortly before birth.

In this series two distinct varieties of childhood leukemias were identified: (1) prezygotic and (2) prenatal. It is postulated that the role of leukocytes in pyogenic infections and the profound changes which have followed the introduction of antibiotics have led to the discovery of a variety of leukemia in which the first decisive event predates conception and produces a preleukemic gene. The prezygotic leukemias derived from these genes are responsible for the early peak of leukemia mortality (2-4 years) and they have their counterpart in other cancers. It is suggested that in any population the numbers of preleukemic genes and of prezygotic leukemias are controlled to a large extent by the prevalence and mortality of pyogenic infections.

It is proposed that these findings as a whole suggest a "two-event" scheme of development of malignant disease. The *initial or predisposing event* in every case is a gene mutation; this may eventually result in *prezygotic or inherited cancers*, or in *postzygotic or acquired cancers*, depending on whether the original mutation occurred in a germ cell (prezygotic) or a somatic cell (postzygotic). *Secondary or precipitating events*, representing conditions of "cell stress", may be needed to convert "precancer cells" into cancer cells. In the case of prezygotic cancers there is a danger that a pre-cancerous state may be transmitted to future generations; in postzygotic cancers there is no such danger.

F.L.

#### THE COST OF MORTALITY

THERE are various ways in which deaths in a community can be studied. The usual way is in the form of a rate, usually per 1000, or per 100,000 persons at risk, per annum. A more realistic approach is that which is concerned with "working years lost", or "years of life lost", due to death from disease or accident.

The Division of Medical Statistics of the Ontario Department of Health has recently reported a survey of this type, entitled "A Study of the Loss of Expected Years of Life due to Certain Causes, Ontario". The data are calculated for three separate periods around three census years, 1931-33, 1941-43, and 1951-53.

The accompanying table has been calculated for the latter period, for males, assuming an average loss of \$3000 per working year.

AVERAGE NUMBER OF DEATHS BY CAUSE, WORKING YEARS LOST, AND  
ESTIMATED COST OF SUCH LOSS, ONTARIO, 1951-53

Cause of death	MALES				
	Number of deaths	Working years lost	Money value of working years lost: constant 1961 dollars	Average working years lost per deceased person	Average money loss per person: constant 1961 dollars
Cardiovascular-renal disease.....	13,295	40,738	122,214,000	3.07	9,210
Cancer, all forms.....	3,414	16,760	50,280,000	4.91	14,730
Pneumonia, bronchitis, influenza.....	1,064	12,042	36,126,000	11.32	33,960
Tuberculosis, all forms.....	287	3,305	9,915,000	11.52	34,560
Diabetes mellitus.....	226	1,416	4,248,000	4.52	13,560
Communicable diseases.....	26	956	2,868,000	36.77	110,310
All accidents.....	2,037	45,314	135,942,000	22.25	66,750
(Motor vehicle accidents).....	(774)	(17,900)	(53,700,000)	(23.13)	(69,390)
Suicide.....	310	4,674	14,022,000	18.08	54,240
Certain diseases of early infancy.....	1,216	46,190	138,570,000	37.99	113,970
All other causes.....	3,102	45,768	137,304,000	14.75	44,250
Total or average.....	24,977	217,163	651,489,000	8.69	26,084

In spite of the fact that many people die from cardiovascular-renal disease, the average number of working years lost in males due to this group of diseases is 3.07. A similar situation applies in relation to cancer and diabetes mellitus which are, in general, diseases of older people.

The diseases that inflict the greatest financial loss on individual males and their families are: "all accidents", "motor vehicle accidents", and "suicides". Communicable diseases and certain diseases of early infancy involve a loss to the individual himself, but hardly to his potential family, which of course could not exist if he did not survive to maturity.

To those who deplore the costs of total health care, which are at present in the region of \$100 per head per annum in Canada, one would point out that the average cost of a male death in terms of loss of potential earnings is \$26,084. Even a whole lifetime of 70 years, at constant 1961 dollars, would involve only \$7000 in total health care. So, perhaps, after all, it is cheaper to live than to die.

W.H.LER.

#### MEDICAL TREATMENT FOR NON-PATENT FALLOPIAN TUBES

**P**ROBABLY one of the most interesting, time-consuming, and yet rewarding problems encountered in practice is that of the infertile couple.

Successful results depend directly upon the interest and intensity of investigation of the attending physician. It is generally accepted that any couple who earnestly desire children and have not conceived within one year should be fully investigated. It is to be remembered that many barren marriages are due to the union of two persons of low fertility capabilities rather than to a complete defect of one partner. Mazer and Israel<sup>1</sup> list five important etiological factors of which the majority are easily diagnosed and easily treated. These, briefly, are (1) the presence of grossly recognizable

pelvic disorders, (2) the possibility of cervical and uterine insemination, (3) the condition of the fallopian tubes, (4) the state of fertility of the male and (5) the endocrine stability of the female. Appreciation of the need for maximum investigation when necessary and a minimum of surgical intervention warrants considerable attention and emphasizes the old adage that "there is more to the problem of sterility than potent males and patent tubes."

Surgical procedures which have been advocated range from simple dilatation of the cervix to radical tuboplastic procedures or multiple myomectomies. The frequency of utilization of surgical procedures in patients with fertility problems depends upon the persistence of the infertile couple and the enthusiasm of the attending physician. Evidence suggests that repeated hysterosalpingograms have a therapeutic effect upon women with non-patent fallopian tubes and considerable success has followed this diagnostic procedure.

It now appears that, should the diagnosis of occlusion of the tubes be made by salpingogram on two occasions, whether a hydrosalpinx is present or not, the administration of prednisolone may be efficacious in relieving the obstruction.<sup>2</sup> The usual precautions should be undertaken before and during administration of corticosteroids. Some authors use the uterotubal route, whereas equally satisfying results have been obtained by oral administration of 10 mg. of prednisolone daily, supplemented by 25 mg. intramuscularly twice weekly. This treatment is recommended for a period of three to six months and should certainly be utilized before any tuboplastic operation is attempted.

W.F.B.

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## LETTERS TO THE EDITOR

### RADIOLOGY OF THE ABDOMINAL AORTA AND RENAL ARTERIES

To the Editor:

A recent Medical News in Brief item entitled "Intravenous Aortography" (*Canad. M. A. J.*, 84: 738, 1961) does not mention visualization of the abdominal branch arteries. There is a tendency to assume that whatever method of aortography is used, satisfactory demonstration of the aorta will result in demonstration of its major branches.

This is not so, as reference to page 1265 of the present issue will reveal. In the article referred to, Hemley, Arida and Ring<sup>1</sup> state that in their experience intravenous aortography has consistently failed to demonstrate the renal arteries adequately. They also indicate that in many cases translumbar aortography fails to visualize the renal arteries, particularly the left. They note that the hazards and problems of translumbar aortography are a matter of general knowledge, though in this latter respect they are possibly being over-generous. Aortic dissections may go unnoticed, and even fairly large dissections may be impossible to detect if only one or two films are taken. The appearances indicating dissection may only be seen on the last of several serial films after the aortic lumen has cleared itself of contrast medium.

Furthermore, unilateral renal damage can hardly be entirely excluded unless differential renal excretion and blood pressure follow-up studies are made for some time after the examination; these are frequently not done.

Preliminary reports of the intravenous technique looked promising to those interested in renal angiography. Subsequent demonstrations and articles, including the recent one by Hemley, indicate that it is disappointing for this type of work.

There are now three major means of aortography, namely the percutaneous transfemoral method, translumbar aortography and intravenous aortography, and it is becoming apparent that there is no single best method to use in every instance.

The technique chosen for any given patient should therefore be that indicated by individual circumstance.

The growing literature from most parts of the world since Seldinger's article in 1953<sup>2</sup> indicates that for the demonstration of the aorta, and particularly its branches, the percutaneous transfemoral technique is very much preferable to other methods. The results are better and more safely obtained, and the patient is more comfortable and able to co-operate. This has certainly been my experience.<sup>3</sup>

There are, nevertheless, patients with arteriosclerotic disease in whom the transfemoral route may be contra-indicated because of tortuous iliac arteries or occlusive vascular lesions.

For the specific assessment of occlusive aorto-iliac disease the intravenous technique may thus have much to offer, especially if there is no great reason to demonstrate the renal arteries well.

If conversely, the examination is directed particularly to the renal arteries in patients with severe arterio-

sclerotic aorto-iliac disease, translumbar aortography would still appear to have a place.

Consequently I believe that everyone performing angiography of the aorta and its branches should become skilled with more than one method, though I also believe that the more experienced they become with the transfemoral technique, the less use they will have for the translumbar one.

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### HAZARDS AND HINDRANCES IN PSYCHIATRIC RESEARCH

To the Editor:

I would like to record my appreciation of Dr. Cleghorn's paper "Hazards and Hindrances in Psychiatric Research" (*Canad. M. A. J.*, 84: 834, 1961). I found it a wise and thought-provoking discussion of a subject which receives much lip service but too little understanding. I appreciated the many shrewd observations, some of which are pertinent beyond the realm of psychiatric research, but I must confine my comments to two matters.

My first point is that in thinking of how to find and educate research workers, we should draw on existing potential and beware of instituting a progressive course which can only be entered at the beginning.

While it is true that research and treatment are best served by different capacities, as noted by Lewis and others, nature seldom provides personalities which can happily be assigned either to research or to treatment. It seems likely that some of the described traits from each category may be held by the same individual, the appropriate ones being called forth by the demands of the working situation. One imagines some of our great clinical investigators to have been of that kind. If this is true it would seem that, while spotting of research talents should begin early and while suitable encouragement and training ought to be provided, it should not thus become an exclusive road to research work, a road with only this starting point.

I would like to see opportunity available for some movement between the whole-time research and the whole-time therapeutic fields. I believe that some therapists, while not wishing to devote themselves to research altogether, do possess research talent which should be encouraged. Likewise, I imagine that there might be times when a research worker might desire and even profit from a stimulus period of therapeutic endeavour. Such movement at present appears to be hampered more by administrative and financial difficulties than by individual choice.

Secondly, it has often been noted that mental hospitals have a wealth of clinical material available but usually no research personnel. Presumably this material could be used by researchers if available to them. If it is true that there is some research talent among those currently working solely as therapists, could they not be used as the link, by being encouraged to do some or all of the field work under the guidance of the full-time researcher? One can envisage the initial steps being taken from either side. From the hospital side it would begin as an idea for a study perhaps suggested by the nature of the clinical material. The problem would be to find a research worker interested in that kind of problem. From the research centre, it would begin as a plan for research which required clinical material or facilities not available locally. Here the problem would be to find a hospital where the material was available. If it was thought suitable and a staff member was interested, he might be used in the project. Some means of communication would seem to be needed to facilitate this kind of co-operation. I have little doubt that most researchers would be willing to respond to any request for advice and guidance, but the hospital worker distant from the large centres has the handicaps of not knowing whom to approach and of being diffident about making the approach—partly because of being afraid to waste valuable time and partly because of the fear of rebuff. The research worker, for his part, might be inhibited by uncertainty about hospitals' reactions.

Since I represent the hospital side, I would be interested in hearing research workers' reactions to such a proposal. The interchange might be initiated by invitations to researchers from the hospitals to make occasional visits in order to talk about their own research work, and also to meet and talk with the hospital staff. I believe that such mutual co-operation, if it could be achieved, could be of great value to both the clinical and research fields.

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#### WINDS OF CHANGE IN MEDICAL CARE

To the Editor:

While we do not yet know the terms of reference of the recently announced Royal Commission on Health Services, we sincerely hope that it will not be another political tinkering job, but a full examination of health needs of the country and its people.

Such a commission would need to examine the whole present basis of medical services. As we see it now, there is increasing emphasis on building more hospital accommodation, whether communities need it or not. We need much more clear thinking on such issues as diagnostic centres, clinics, group practices, or other units physically removed from hospitals, provision of beds for long-term patients, facilities for rehabilitation, and provision for the aged.

Old people do not necessarily want to live in large institutions. Why should we not build more low-rental apartments for older people, close to the centre of the

city? Why do we not show a little imagination and humanity in dealing with older people? Why do we not make a more active attempt to provide home nursing services? Why is there this state of mental block in the minds of physicians, hospitals, provincial governments, and medical officers of health? In a recent issue of the *Medical Services Journal*, an account appears of three home care plans in Canada, one in Toronto under the direction of Dr. L. A. Pequegnat;<sup>1</sup> another from Reddy Memorial Hospital, Montreal, under Dr. E. R. Gubbay and Dr. T. L. Barry;<sup>2</sup> and a third from the Ottawa D.V.A. Hospitals, described by Miss Freda Johanneson.<sup>3</sup> There is no need of further experimentation in this field. We need implementation of these principles on a large-scale provincial basis.

Recent announcements by the chairman of the Ontario Hospital Services Commission concerning actual and potential increases in the costs of operations of that Commission are undoubtedly startling. This raises the point that no country in the world can afford to spend disproportionate amounts of income on medical services, whatever the wild-eyed visionaries may say. We can only spend if we produce, if we increase our national output. This we have not done in the last few years.

At a conservative estimate complete medical, dental, pharmaceutical, nursing and public health services would cost at least \$100 per head of population per annum. This means a sum of \$1,800,000,000 for 1961, and considerably more in succeeding years. Let it be noted that this would be the cost if all services were prepaid at present rates.

In taking a national view it is clear that the needs of education, research, agriculture, roads, and general economic development, to name but a few important fields, possibly even national defence, must take precedence over medical care.

If we do not cultivate the brains of our people, there never will be enough money to look after their bodily ills. The resurgence of Europe after the last war is as much due to economic development as to the inventiveness and skills of its population. We fear that Canadians in general have not yet realized that North America needs to pull up its socks smartly if it is not to be outstripped in all fields, not by the much publicized Soviet Union, but by Western Europe and Japan.

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## MEDICAL NEWS IN BRIEF

### RADIOGRAPHIC METHODS OF OPACIFICATION OF THE RENAL ARTERIES

A study of the available methods of renal arteriography recently reported by Hemley, Arida and Ring (*Radiology*, 76: 402, 1961) led the authors to believe that the percutaneous retrograde femoral catheter method is the only complete and precise procedure for visualization of the renal arteries.

The value of intravenous abdominal aortography is discussed, and the authors feel that, having carried out over 25 such studies, a widespread misconception has resulted as to its usefulness in demonstrating the renal arteries. In their hands it has consistently failed to demonstrate these arteries with sufficient clarity, and it is inadequate for the demonstration of structural changes within them.

Translumbar aortography is also considered inadequate and fails to opacify the left renal artery in a significant number of cases; they also believe this to be an inherent technical deficiency in the procedure. In a series of 127 abdominal aortograms the renal arteries were incidentally visualized in only 40%. An additional 15 such examinations were performed specifically for the study of renal disease and only nine of these were diagnostic.

Apart from these inadequacies, translumbar aortography is dangerous from the standpoint of renal toxicity. The papers of Crawford *et al.* and of Miller *et al.* are quoted, the former referring to 12 cases of unilateral renal damage, and the latter reporting a 3% incidence of renal damage.

The authors' experience, substantiated by an analysis of current literature, indicates that the safest, most practical and technically the most adequate method is that of catheterization of the aorta by the percutaneous femoral approach.

It is also noted that the usually applied renal function studies, including the differential salt excretion test, are often inconclusive and even misleading. [See also Letters to the Editor on page 1263 of this issue.—Ed.]

### THE TREATMENT OF CEREBRAL PALSY

Treatment of cerebral palsy is complex, involving many methods and many people. Surgical treatment, by both operative and non-operative methods, although generally held in poor regard, has an important place in the treatment of the brain-injured child (*Proc. Roy. Soc. Med.*, 54: 146, 1961). A detailed description of the treatment of a cerebral-palsied child with equinus deformity indicates that even such a seemingly simple problem as equinus becomes complex when the underlying cause is cerebral palsy. The choice of method of treatment depends on a careful appraisal of the mechanical disability present in relation to the child as a whole; one method is not applicable to all cases.

No ideal method of treating hypertonus has yet been found: procaine injections into motor points are too transient in their effect; drugs such as Trancopal and Tigloidine have not produced any significant im-

provement; injections into theca and other structures are exacting procedures and may produce serious complications if not done correctly (*Ibid.*, 54: 143, 1961). Treatment of any involuntary movements which occur is necessary. Stereotactic procedures (chemopallidectomy or chemothalamectomy) have not proved successful in abolishing choreoathetosis in cerebral palsy cases. Topectomy, with ablation of both area 4 and area 6, can be permanently successful in the treatment of unilateral (or mainly unilateral) athetosis. In some cases amputation of a limb severely affected by athetosis, with subsequent provision of an artificial limb can produce excellent results. In addition, the many defects which are commonly associated with cerebral palsy, such as hearing and ocular defects, can and should be treated.

Accurate assessment of the progression of cerebral palsy patients having treatment and training has always been a problem. An objective test, the poly-electromyograph, can now provide a qualitative and quantitative record, on paper, of a motor disability before and after some therapeutic procedure.

### HEALTH AND ECONOMICS IN MAURITIUS

Better health means an increasing population which, in many countries, the existing economy cannot support. In Mauritius two recent reports to the Governor describe the difficult situation there and suggest solutions; these are discussed in a leading article in the *Lancet* (1: 542, 1961). It seems that public health measures in Mauritius, as elsewhere, are saving lives and reducing general mortality. The present trend is towards doubling their population by 1982. Further, the age structure is changing. Soon half the population will be dependants under 15 years of age (the comparable figure in north-west and central Europe is only a quarter); and to make things worse, the island's economy depends essentially on one crop — sugar. In this regard, fluctuating world prices and seasonal work can bring about increased unemployment.

One of the reports to the Governor (by Titmuss, Abel-Smith and Lynes) states that the essential solution lies in family planning; this is strongly urged despite the fact that nearly half the population of Mauritius is Roman Catholic. The report includes detailed and valuable proposals on social security benefits, but the group plead that unless these are accompanied by a family-planning service they would prefer to see the report rejected. The "three-child family" is the basis of the proposals, with an insistence on later marriage and financial support for families who space their children, and no additional benefits for dependent children in excess of three.

The only answer to the dilemma of the present and the future in Mauritius would seem to lie in family planning. What the community will decide to do in this matter will be awaited with interest.

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## MEDICAL MEETINGS

### EIGHTY-FIRST ANNUAL MEETING, ONTARIO MEDICAL ASSOCIATION

That the Ontario Medical Association convention now constitutes one of the largest regular medical gatherings in Canada was amply evident at the eighty-first annual O.M.A. meeting which was held at the Royal York Hotel in Toronto, from May 7 to 12. During this six-day period, some 1870 registrants were (1) educated through the medium of 72 papers and six panel discussions presented at five general scientific sessions and at 17 clinical meetings of various sections of the Association, (2) nutritionally replenished at five official luncheons and the annual O.M.A. dinner, (3) brainwashed at an exhaustive series of business meetings, and (4) entertained by a wide-ranging program of social activities.

#### BUSINESS MEETINGS

Sessions of the O.M.A. Council were held on the afternoon of Sunday, May 7, the morning, afternoon and evening of Tuesday, May 8, and the morning and afternoon of Wednesday, May 9.

The Annual Business Meeting of the Association was conducted on Wednesday, May 10, and the Board of Directors met on Thursday, May 11.

In addition, the Committee on Nomination held a meeting on May 7, as did the Maternal Welfare Committee on May 10.

Business meetings of 23 sections of the Association were scheduled on May 11 and 12.

#### SCIENTIFIC SESSIONS

##### *General Session—Wednesday Morning, May 10*

The opening general session was devoted to a symposium on "The Diagnosis and Treatment of Surgical Heart Conditions" under the chairmanship of Dr. H. Garfield Kelly, Associate Professor of Medicine, Queen's University.

The first paper, entitled "Diagnosis of Congenital Heart Disease", was delivered by Dr. R. S. Fowler of the Toronto Hospital for Sick Children and the University of Toronto. Dr. Fowler's discussion was largely devoted to the clinical, radiological and electrocardiographic features of common congenital heart lesions, particularly atrial and ventricular septal defects, patent ductus arteriosus, the tetralogy of Fallot and coarctation of the aorta.

Dr. George Manning, Associate Professor of Medicine, the University of Western Ontario, discussed the diagnosis of those forms of heart disease that are amenable to correction or alleviation by surgical procedures. Dr. Manning's contribution to the symposium was illustrated by an impressive demonstration of what the educationalists call audiovisual teaching techniques involving a motion-picture film of scintillating electrocardiographic tracings to the accompaniment of a sound track of the simultaneously recorded phonocardiographic grindings, rumbles, roars and swooshes picked up by a microphone inserted on the end of a cardiac catheter into the various heart chambers and great vessels.

Dr. William T. Mustard, Assistant Professor of Surgery, University of Toronto, and Associate Surgeon at the Toronto Hospital for Sick Children, in his presentation on the "Surgical Management of Congenital Heart Disease" traced the development of this rapidly expanding area of surgery since 1938 when Gross demonstrated the feasibility of a surgical approach to the treatment of patent ductus arteriosus, followed shortly thereafter by the important pioneer contributions of Blalock and Taussig. Cardiac surgery, now barely entering its third decade of development, still leaves a great deal to be desired but appears to be steadily improving in technical perfection and practical applicability. In this particular branch of surgery the solo virtuoso has been replaced by a team which, in addition to the surgeon, includes the cardiologist, anesthesiologist and specially trained nurses and technicians, all of whom render contributions that are indispensable to the success of preoperative, operative and postoperative management of the cardiac surgical patient. Dr. Mustard concluded his remarks with a discussion of various aspects of surgical technique in the treatment of such congenital lesions as septal defects, patent ductus arteriosus, pulmonary stenosis, coarctation of the aorta and the tetralogy of Fallot, and outlined the results of such treatment in his experience to date.

The final paper of this symposium, on the subject of "Other Cardiac Surgery", was delivered by Dr. John C. Coles, Assistant Professor of Surgery and Chief of the Department of Cardiovascular Surgery at the University of Western Ontario. Dr. Coles' presentation concerned the surgical treatment of such non-congenital disorders as rheumatic lesions of the mitral and aortic valves, calcific aortic valve disease, and luteal and arteriosclerotic aneurysms of the thoracic and abdominal aorta. He pointed out that surgical procedures for coronary artery disease are largely confined to coronary endarterectomy, repair of ventricular aneurysms which develop after myocardial infarction, and adequate thoracic sympathectomy for relief of intractable angina pectoris. The results of these procedures leave much to be desired at the present time. He also briefly discussed the role of hypothermia in open heart surgery and summed up his comments with the observation that, in general, surgical procedures for acquired heart disease, while not as gratifying as those employed in treatment of many congenital heart lesions, may have much to offer in certain carefully selected cases.

The symposium closed with a panel discussion in which the chairman and all of the speakers participated. Evaluation of various types of heart murmurs in school children, and the role of German measles in relation to congenital heart disease, received considerable comment. It was agreed that gamma globulin should be administered to any pregnant woman exposed to rubella infection. The panel noted that while the overall incidence of rheumatic fever appears to be declining in recent years there is as yet no good evidence of a decrease in prevalence of rheumatic heart disease. The value of antibiotic administration in the prophylaxis of rheumatic fever recurrences was emphasized. There was general agreement that, barring specific contraindications in individual cases, patients with aortic stenosis or insufficiency, and those with mitral stenosis,

who were reasonably good operative risks and who were deteriorating despite conscientious attention to medical treatment, should be subjected to operation with reasonable expectation that some degree of palliation at least could be provided.

#### *General Session, Wednesday Afternoon, May 10*

A symposium on "Current Trends in Treatment" was presented under the capable and articulate chairmanship of Dr. R. K. Magee, of the surgical staff, St. Joseph's and Civic Hospitals, Peterborough. In his introductory remarks he commented on the explosive advance in disease concepts during this century, with emphasis on the remarkable developments in the field of antibiotics and chemotherapy, ranging from Ehrlich's discovery of 606, through the development of the sulfonamides, penicillin and a vast galaxy of broad-spectrum and specific antibiotics.

Dr. W. Bruce Barton, Instructor in Medicine at the University of Western Ontario, in his discussion of "Chemotherapy in Medical Disease" commented on the use of antitumour chemotherapeutic agents, pointing out that this is by no means a recent development. As early as 1865 potassium arsenite was used in the treatment of leukemia and the lymphomas. In 1942 a patient was treated with nitrogen mustard for the first time. In 1946 it was shown that urethane has some effect on carcinoma and leukemia, and in 1948, Farber demonstrated that certain folic acid analogues exerted an influence on acute leukemia. Between 1948 and 1959 a series of alkylating agents in addition to nitrogen mustard have been shown to possess antitumour activity. In 1949 and 1950, Pearson demonstrated that remissions may occur in some patients with acute leukemia and chronic lymphatic leukemia following administration of corticosteroids. By 1954 it was recognized that the antibiotics, actinomycin C and D, exerted an antineoplastic effect on certain forms of cancer, notably on Wilms' tumour. Subsequently, it was discovered that antitumour activity is also possessed by the fluorinated pyrimidines.

To date, the screening of drugs employed in the chemotherapy of cancer has remained on an empiric basis. Though this is far from satisfactory, it is the only method by which such screening can be conducted at present.

The *alkylating agents* act by damaging many cell constituents, of which DNA appears to be the most vulnerable. The effects of the various drugs in this group appear to be essentially similar upon similar clinical disorders. There is no evidence as yet that they prolong survival to a significant degree. All of the agents in this series can cause some bone marrow depression. Nitrogen mustard, the first and most widely used of the alkylating compounds, is administered intravenously, intra-arterially or by local injection of body cavities or tumour sites. As in other drugs in this group, its antitumour activity lies in its ethyleneimonium configuration (the alkylating component). Nitrogen mustard appears to be of greatest value in the treatment of patients suffering from Hodgkin's disease with constitutional manifestations and no lesions amenable to local therapy. It is also of some benefit in some of the other lymphomas and cancer of the ovary and the lung.

Chlorambucil (Leukeran) has some effect upon all disorders that are influenced by nitrogen mustard but

its greatest effectiveness appears to result from the treatment of chronic lymphatic leukemia. It can be given either orally or parenterally but its administration requires considerable caution.

Tri-ethylene melamine (TEM) is gradually being replaced by other alkylating agents in clinical therapy.

Endoxan is used largely for treatment of the lymphomas, particularly reticulum cell sarcoma. Alopecia of some degree has been reported in 10 to 30% of persons treated with this drug.

Thio-TEPA is useful for intravenous administration and for instillation into cavitory spaces. It causes less local inflammatory reaction and has less tendency to induce venous thrombosis after intravenous injection than other drugs in this group.

Phenylalanine mustard may be of some value in the treatment of occasional cases of melanoma.

Myleran has proved to be of benefit in the treatment of chronic granulocytic leukemia and possibly of polycythemia rubra vera, as well.

*Antimetabolites* are compounds with a chemical constitution very similar to that of substances essential to normal metabolism. Of the antifolic agents, amethopterin is the most familiar prototype. This drug has some value in treatment of testicular tumours, particularly choriocarcinoma, and in choriocarcinoma in females, but its main field of usefulness is in the treatment of acute leukemia in children. Should the toxic side effects of this drug reach serious proportions, citrovorum factor is a most effective and rapidly acting antidote. The prototype of the purine analogues is 6-mercaptopurine. The most effective use for this drug is in the treatment of acute leukemia, especially in adults. 5-Fluorouracil is a comparatively recently developed antitumour agent, the effects of which have been investigated largely in cases of carcinoma of the breast and of the intestinal tract. Treatment with this drug may be very difficult to manage. Among its particularly serious side effects is an overwhelming cholera-like syndrome. This drug may be of some practical therapeutic value when used in conjunction with roentgen therapy.

The *antibiotics* with antineoplastic properties are also difficult to manage. Those available to date have to be given intravenously; they commonly cause bone marrow depression and they have a marked tendency to produce venous thrombosis. They may be of some value in the treatment of testicular choriocarcinoma or of Wilms' tumour.

A miscellaneous group of antitumour agents includes the corticosteroids; urethane, which is of benefit in some cases of myeloma; and vincalkebostine, which has been noted to produce distinct but brief remission in choriocarcinoma.

Dr. Barton summarized his comments with the observation that, to date, chemotherapeutic agents have produced no known cures of any malignant neoplasm but that there have been some exciting and dramatic palliative results from treatment with these drugs. Despite the tremendous research effort and expenditure that has been and is being channelled into this field, Dr. Barton felt that the likelihood that it will produce a major breakthrough in cancer therapy is remote. A more likely area of breakthrough, in his opinion, is that of basic cellular physiology and biochemistry. He observed that there is still a long way to go in cancer therapy, that all available chemotherapeutic substances are double-edged swords with potentially devastating

and sometimes lethal side effects, and that radiotherapy is still at least as effective, or more so, in the great majority of cases of malignant disease.

Dr. John A. McCredie, Instructor in Surgery at the University of Western Ontario and Research Fellow of the Ontario Cancer Institute, in his discussion of "Chemotherapy in Surgical Disease" commented that despite rather striking refinements in surgical techniques in recent years there has been little noticeable improvement in the results of surgical treatment of cancer.

There is evidence that some cancer cells are left in surgical incisions in about one-quarter of patients operated upon for malignant disease or subjected to the insertion of needles or surgical instruments into tumours for biopsy or any other reason. Not all of these cells survive, spread or metastasize but it is nevertheless important to recognize the possibility and frequency of their presence. For this reason investigations have been conducted regarding the effectiveness of irrigation or local application of anticancer agents in the wounds of patients subjected to operation for cancer. Clorpactin and nitrogen mustard, for example, have been employed for this purpose but there is evidence that nitrogen mustard impairs wound healing, so that its local use in wounds has now been pretty well discarded.

To date, no drugs have been discovered which will prevent lymphatic spread of cancer cells.

As far as blood spread is concerned, it has been reported that cancer cells can be demonstrated in the blood stream of about one-third of patients with cancer and in about half of those subjected to operation involving the tumour site. In the latter, the number of cancer cells in blood draining the immediate area of the tumour is even greater, in the postoperative period. Anaplastic cell types tend to spread in the blood with greater frequency than the more differentiated types. The presence or absence of cancer cells in the blood is, however, of no value in the ultimate prognosis. Manipulation of tumours at operation significantly increases the extent of entry of malignant cells into the blood stream. After administration of nitrogen mustard intravenously in tumour-bearing experimental animals, cancer cells disappear temporarily from the blood stream but tend to reappear later. Nevertheless, experimentally, nitrogen mustard administration does result in a decrease in the incidence of metastases of certain tumour types. In one clinical study a series of patients with breast carcinoma treated by nitrogen mustard showed a lower incidence of postoperative recurrences after mastectomy. Similar results have been reported in patients with breast carcinoma treated with Thio-TEPA and 5-fluorouracil but these drugs are too toxic to permit their widespread and effective use.

With regard to spread of tumour in the lumen of viscera, a significant number of patients develop recurrence in the suture line of anterior resection of carcinoma of the rectum. While this suggests that such recurrences might be controlled by local irrigation of the site of resection with chlorambucil or other anti-tumour agents, it is too early to assess the results of such measures.

In a study of the degree of control of transperitoneal spread of tumour cells now being conducted at the London Cancer Clinic, nitrogen mustard has been administered to a series of patients subjected to operation for intra-abdominal cancer. In this group the drug was

delivered into the lumen of the bowel, the operative wound and the peritoneal cavity. In a second group of patients operated upon for cancer outside the abdomen, nitrogen mustard was administered intravenously, and locally in the operative wound. Local application of nitrogen mustard to the operative site has now been discontinued, since it was found that wound infection was increased and healing was impaired in cases so treated. In this study there was no apparent increase in postoperative morbidity except in association with the intravenous administration of nitrogen mustard which was associated with nausea and vomiting in many instances. Leukopenia was also noted only in those patients who were given this drug intravenously. Dr. McCredie reported that it will be some time before the results of this study can be fully assessed and before any conclusions can be drawn regarding the effect of these measures on the incidence of metastases.

Nitrogen mustard and other anticancer agents such as methotrexate can also be infused intra-arterially. Continuous infusion should be more efficacious but such a procedure is much more difficult to manage than single or repeated infusions. In the event of serious toxic reactions to methotrexate, citrovorum factor is a most effective antidote, and autogenous marrow infusions may mitigate the marrow-depressing effects of the antitumour drugs in general.

Another surgical technique for cancer chemotherapy involves the arterial perfusion of the neoplasm using extracorporeal circulation to isolate the local tumour-bearing area. This procedure provides a maximum concentration of the agent at the tumour site with a minimum amount in the systemic circulation. To date, it has been used largely, but not entirely, for malignant neoplasms in the limbs, and its main practical advantage has been the palliation of advanced, widespread tumours in the extremities. Radiation therapy may be used in combination with perfusion of anticancer drugs. The results of perfusion in association with surgery are still too scanty for adequate evaluation.

The systemic administration of antitumour agents for advanced, widespread malignant disease is essentially a palliative procedure.

In conclusion, Dr. McCredie observed that the chemotherapy of "surgical" malignant disease has not proved to be as beneficial as it was hoped that it would be, a few years ago. Nevertheless, some progress has been made in this field. Major difficulties are presented by the fact that damage to normal tissues is so extensive if the anticancer agents are used in amounts and concentrations sufficient to affect significantly the tumour itself.

Dr. N. M. Wrong, Associate Professor of Medicine in charge of Dermatology at the University of Toronto, then presented an exhaustive and impressively illustrated "Critical Appraisal of Griseofulvin in Dermatology". He noted that critical evaluation of a new drug usually takes a minimum of about two years, during which a large amount of initial hyper-enthusiasm wears off, permitting a more sane and rational assessment of the practical therapeutic value of the agent in question. Such has been the case with regard to griseofulvin, a product of *Penicillium griseofulvum* and other penicillia, which was first used clinically in 1958 after Gentle's report of its curative effect on ringworm infections in guinea pigs. Since that time it has been widely used throughout the civilized world in the

treatment of many thousands of patients with a variety of disorders. From a study of the reports to date, the following facts emerge. No deaths have as yet been reported from its use. Reactions such as nausea, vomiting, abdominal distension, headache and dizziness occur fairly frequently, and sometimes the use of this antibiotic must be discontinued because of the severity of these reactions. Leukopenia has been reported but the leukocyte count returns to normal quickly even when administration of the drug is continued. Griseofulvin given orally in dosage of one tablet (250 mg.) two to four times daily is the only treatment of real value for *Trichophyton rubrum* infection of the palms, soles and nails. It has also controlled *Tinea capitis* (ringworm of the scalp) without the necessity of x-ray depilation of scalp hair, although its effect may be slow. It has been rather disappointing in the treatment of *Trichophyton* infections of the scalp and beard area. It will not "cure" fungous infections of the interdigital webs between the toes and is probably not superior to topical remedies for this purpose. It has controlled or cured some very severe and bizarre *Epidermophyton* and *Trichophyton* infections encountered in the tropics and sub-tropics. It has no effect on the deep mycoses or on moniliasis (Candidiasis).

It is hoped that the discovery of griseofulvin may pave the way for the development of other antibiotics which may be of superior value in treatment of superficial fungous infections and control of deep infections, in a fashion comparable to the manner in which penicillin paved the way for the production of a host of other useful antibiotics.

The final paper of this symposium, entitled "Updating Antibiotic Therapy", was delivered by Dr. Douglas G. Cameron, Physician in Chief, Montreal General Hospital, Professor of Medicine and Director of McGill University Medical Clinic of the Montreal General Hospital. This timely, important and scholarly address will be published in its entirety in a forthcoming issue of this journal, and is recommended as required reading for all who practise in any area of clinical medicine or surgery.

#### General Session—Thursday Morning, May 11

The symposium on "Hemorrhage in Obstetrics" was chaired by Dr. H. R. de St. Victor, Professor of Obstetrics, the University of Ottawa. In his introductory remarks Dr. de St. Victor commented that the importance of this subject is evidenced by the fact that of the 1395 maternal deaths in Canada between 1954 and 1955, 365 (26%) were due to obstetrical hemorrhage.

Dr. P. Bruce-Lockhart, Chief of Obstetrics at the Sudbury Memorial Hospital, opened the symposium with a discussion of "Abruptio Placenta". Separation of the normally implanted placenta generally presents in the form of antepartum hemorrhage, usually accompanied by some degree of pain. The textbook picture of a woody hard uterus in a patient suffering from severe cardiovascular collapse is an important but rare manifestation of this disorder. In most instances the diagnosis is actually made on postpartum examination of the placenta. There appears to be an association of abruptio placenta with hypertension and toxemia but which is the cause and which the effect is still not clear. O'Donnell at the Dublin Rotunda reported that the incidence of abruptio placenta was essentially the

same among general admissions as it was among patients with toxemia. Tachycardia is an important physical sign which should be watched for in addition to hypertension and uterine spasm. Regarding the controversial question of whether patients with abruptio should be treated conservatively or by Cesarean section, Dr. Bruce-Lockhart expressed the personal view that Cesarean section is rarely required for abruptio placenta only, and that this operation rarely results in saving a baby who would not have survived in any event had the mother been treated conservatively. Patients with abruptio placenta complicated by toxemia, with delayed dilatation of the cervix, probably do require Cesarean section. An essential feature in the treatment is, of course, the replacement of blood loss by transfusions, and the general measures of treatment for shock. When the latter is controlled, the membranes should be ruptured whether or not uterine contractions have already begun. In some cases there is accompanying hypofibrinogenemia with defective clotting which is usually obvious by simple inspection of the patient's blood. When this finding is present there is no need to wait for laboratory determination of the fibrinogen level. If fibrinogen should be available, it should be administered at once; if not, the patient should be adequately transfused with whole blood. In the postpartum period there is still some danger that toxemia or uterine atony may develop as long as four hours after delivery, so the patient should be kept under close observation during this period.

Dr. G. A. Cram, Chief of Obstetrics and Gynecology at St. Joseph's General Hospital, Port Arthur, then discussed "Placenta Previa", which he defined as the implantation of the placenta low enough in the uterus either to overlie or to reach the edge of the internal os of the cervix. This disorder is manifested by bleeding in the latter half of pregnancy, particularly in the last trimester. Its incidence is reported as 1 in 100 to 1 in 200 deliveries, so that the average practitioner may expect to encounter this condition once every year or two. The etiology is unknown except in those patients with an accessory lobe or placenta membranacea. As to diagnosis, any patient with bleeding in the last half of pregnancy, particularly after 30 weeks' gestation, should be suspected of having low implantation of the placenta. Painless, bright red vaginal bleeding is the usual presenting manifestation; the uterus is soft, or if labour has begun it softens between contractions. An abnormal presentation is noted in one-third of cases, the presenting part being higher than usual. Any patient with these manifestations should be admitted to hospital for investigation after cross-matching and typing her blood. If she is over 36 weeks' pregnant, if labour has begun, or if hemorrhage is profuse, a definite diagnosis must be established. The only sure way to confirm this is by intracervical digital examination, never preceded by rectal examination, and always carried out under strict sterile conditions in an operating room with blood available, an anesthetist on hand and facilities available for immediate Cesarean section if excessive bleeding begins or persists. On the other hand, if the patient is less than 36 weeks' pregnant, if bleeding is not profuse and labour has not begun, less radical measures can be adopted to establish a presumptive diagnosis. Careful sterile speculum examination will exclude carcinoma or polyps of the cervix. Palpation of the vaginal fornices may reveal a boggy placenta intervening between the presenting

part and the examining fingers. Finally, where available, soft tissue x-ray techniques in experienced hands can rule out the presence of placenta previa in a high percentage of cases, particularly between 32 and 36 weeks' gestation. Approximately 25% of cases of placenta previa fall within this second group in whom the fetus is not yet mature. An attempt can be made to carry these patients to maturity in hospital unless heavy bleeding intervenes. When fetal maturity is attained, an intracervical digital examination should be carried out in an operating room and a decision should be reached regarding the method of delivery to be undertaken. Basic fundamentals of active treatment include control of bleeding, adequate blood replacement and termination of pregnancy at the optimal time from the point of view of fetal loss and maternal mortality and/or morbidity. All patients with total placenta previa should be delivered by Cesarean section, as should almost all primigravidas with low placental implantation unless the latter is accompanied by only minimal bleeding or unless labour is well established. Bougies, bags, manual dilatation and Braxton Hicks versions are essentially passé. Scalp traction or traction on a foot in small breech presentations may be of use in occasional cases. Usually multipara with low lying placenta, and some with partial placenta previa, deliver satisfactorily and can be induced, near term, by simple rupture of the membranes. Employing the foregoing principles, about 50 to 70% of cases of placenta previa will require delivery by the abdominal route, the so-called classical operation being preferable in view of the greatly increased vascularity of the lower segment and the increased incidence of abnormal presentations. With adequate facilities for blood replacement the maternal loss should be almost zero. Thus, if such facilities are not available, the patient should be referred at once to a properly equipped centre. The overall perinatal mortality still exceeds 15%. A high percentage of these infants die owing to prematurity and the associated respiratory distress syndrome. In recent years recognition of the role of expectant management has constituted the greatest single advance in the treatment of placenta previa.

Dr. de St. Victor, in discussing "Ectopic Pregnancy", noted that this condition caused 49 deaths, or 10% of all maternal deaths in Canada between 1955 and 1959 inclusive. Its incidence varies from 1 in 100 to 1 in 300 pregnancies in different series. About 95% of ectopic pregnancies are tubal; abdominal, ovarian, intraligamentous and cervical pregnancies occur only very rarely. In most cases the fertilized ovum is implanted in the tube because the propelling mechanism and general physiological characteristics of the latter are disturbed by any of a wide variety of pathological and functional disorders including salpingitis, genital tuberculosis, endometriosis, uterine or pelvic tumours, congenital anomalies of the tubes and transperitoneal migration of the ovum. The well-known clinical manifestations include the classical triad of lower abdominal pain, irregular vaginal bleeding and a missed menstrual period. Ninety-five per cent of tubal pregnancies present with lower abdominal pain, often one-sided, as the initial or early manifestation. Irregular vaginal bleeding is an early symptom in over 90% of cases of tubal pregnancy. Shoulder pain is usually a late manifestation but if present is likely to be pronounced. Weakness, faintness and rectal or urinary complaints are occasionally encountered. The history often reveals a record

of sterility, endocrine disorders, previous abortions, or previous abdominal or pelvic operations. One in 10 gives a history of previous ectopic pregnancy. Pelvic examination reveals the important signs of tubal pregnancy, a painful mass in one adnexal region with aggravation of pain on movement of the cervix by the examining fingers. Despite all of these clinical manifestations, 10 to 20% of patients with ectopic pregnancy will be in a state of shock, indicating that tubal rupture or tubal abortion has occurred, before they reach hospital or the operating room. In most of these the diagnosis should have been established before they reached this state. Colpotomy, culdoscopy and culdocentesis are three vaginal procedures of considerable value in establishing the diagnosis of tubal pregnancy. The first two are surgical procedures requiring an operating room; the last is a simple useful procedure that is easy to perform and can be carried out in the physician's office. Cullen's sign is rarely present and is not pathognomonic; expulsion of an endometrial cast is not diagnostic; nor does curettage establish the diagnosis as all phases of the ovarian cycle may be found in the endometrium. Hysterosalpingography and arteriography are now rarely used, though some claim that they are of diagnostic value. In summary, the early diagnosis of ectopic pregnancy remains an important and often difficult problem. The prognosis of tubal pregnancy, though varied, is generally unsatisfactory: 40 to 50% have no further pregnancies though the same percentage will have or have had children; 25% have had or will have abortions; and 10% may expect another ectopic pregnancy. Patients in shock should be admitted to hospital and treated with oxygen and blood transfusions without delay. Definitive treatment of tubal pregnancy involves salpingectomy or salpingo-oophorectomy, the details of surgical technique being a matter of choice of the surgeon concerned. The real problem posed by this disorder is that of early diagnosis. Every suspected case should be immediately hospitalized. The literature of recent years is largely devoted to re-evaluation of old concepts. New procedures for diagnosis are still under study. Improved management and modern surgical techniques have improved the immediate and remote prognosis. However, the incidence of ectopic pregnancy appears to have increased, the diagnosis remains difficult and subject to not infrequent errors and an ever-present mortality toll remains associated with this disorder.

Dr. T. B. Robson, of the staffs of the Metropolitan General, Grace and Hôtel-Dieu Hospitals, Windsor, in a paper entitled "Abortion", described this disorder as the commonest cause of hemorrhage in obstetrics, familiar to all in practice, and usually easy to diagnose and to treat, since antibiotics and transfusions have almost eliminated mortality in spontaneous abortion and cure can readily be effected by the simple procedure of curettage. Dr. Robson devoted his discussion to the 10% of abortions that are not easy to manage and sometimes provide serious trouble. The first problem in this regard is the differentiation of such cases from tubal pregnancy, which should remain a diagnostic consideration in every case of abortion until placental tissue has been identified. Hydatid mole occasionally presents another problem in differential diagnosis in these patients. In 1958, its first year of existence, the O.M.A. Maternal Welfare Committee recorded three deaths due to choriocarcinoma. One of these followed an ordinary incomplete abortion treated by dilatation

and curettage. Those with self-induced or criminally induced abortions are subject to a more serious prognosis. In 1958 and 1959 abortion was second only to hemorrhage as a cause of maternal mortality in Ontario, with sepsis, embolism and renal failure the usual fatal complications. In the case of every patient with abortion admitted to hospital with severe bleeding, shock or evident infection, the possibility of interference should be suspected and the patient should be treated vigorously. The patient who develops shock due to overwhelming sepsis has a grave prognosis and requires immediate treatment with vasopressor drugs, Pitocin, antibiotics and corticosteroids. Blood loss must be replaced and acid-base balance maintained. Oxygen and digitalis may be required to support cardiac action. The urine output must be recorded carefully, since renal failure is almost inevitable. The uterus should be evacuated within 12 hours if possible. *E. coli* and *B. pyocyaneus* are the common offending organisms. Chloramphenicol is the antibiotic of choice. Streptomycin is also effective, though its action is not reliable when it is administered intramuscularly to a patient in shock. Opinions differ regarding the optimum management of less seriously ill patients. If infection is confined to the uterus and products of conception, antibiotics may be administered initially with dilatation and curettage later. Those in whom infection has spread to the adnexa, parametria and peritoneum should be treated vigorously with antibiotics at once and the uterus should be emptied of its grossly infected contents by means of a sponge forceps, within a few hours. Sharp curettage should be delayed until the patient's condition is satisfactorily controlled. Every patient with septic abortion should have a cervical culture and blood cultures should be performed if the infection has spread beyond the uterus. It must be borne in mind that the infected placenta and embryo are beyond the influence of antibiotic drugs administered to the mother.

In cases of missed abortion, if the fetus is beyond 16 weeks' gestation at the time of death and if the uterus has not been evacuated in six weeks, there is a possibility of hemorrhage due to hypofibrinogenemia with its associated coagulation defect. In view of this it is now recommended that the uterus be emptied once this stage has been reached. This may be accomplished by the administration of Pitocin drip, the concentration of Pitocin being gradually increased as required, to initiate uterine contractions.

The final paper in the symposium on obstetrical hemorrhage, entitled "Postpartum Hemorrhage", was presented by Dr. Duncan E. Reid, Chief of Staff of the Boston Lying-in Hospital and Professor and Head of the Department of Obstetrics and Gynecology at Harvard Medical School, following which the chairman and participants in the symposium engaged in an active panel discussion of a number of questions submitted from their large and interested audience.

After an intermission to permit those in attendance to view the exhibits and clinical demonstrations, the session resumed with a paper on the "Current Status of Immunization" by Professor Milton H. Brown, Head of the Department of Public Health, Associate Director of the School of Hygiene of the University of Toronto, and Assistant Director of the Connaught Medical Research Laboratories. Dr. Brown observed that we are living in an age of active immunization in which the use of multiple antigens is widely accepted by the public and by the medical profession. The principle

of combining multiple antigens has many advantages. The speaker provided a far-ranging discussion of a large number of problems and procedures involving the practical value of multiple antigens in immunization of infants and young children, booster doses for school children and the value of combined tetanus-poliomyelitis vaccines; immunization of infants and adults against poliomyelitis; the present status of live, attenuated poliovirus vaccines; immunization against tetanus, smallpox, measles and rabies; and problems of immunization against viral infections such as influenza, the adenoviruses and infectious hepatitis. Professor Brown's extensive discussion may be summarized as follows. A series of multiple antigens is available for the active immunization of infants and children against diphtheria, tetanus, whooping cough and polioviruses of types I, II and III. Young infants with maternal antibodies require more antigen than those without such antibodies. Salk vaccine is very effective when given in suitable dosage. The present need is to actively immunize the entire population. Live attenuated poliovirus vaccine holds promise as an agent of value in the control of paralytic poliomyelitis. Tetanus toxoid should be administered to all age groups to control a serious disease and to eliminate the bothersome use of passive immunization with tetanus antitoxin. Control of smallpox has become a global problem and the population should be kept actively immunized. The control of measles by the use of a live attenuated vaccine is a realistic possibility. Recent findings in the prevention of rabies in man have introduced the use of serum for early passive immunization followed by daily injections of vaccine; a non-neural rabies vaccine is coming into use. Acute respiratory virus infections have assumed an important role in producing increased morbidity and mortality. Viral influenza vaccine has been shown to be of value in certain situations. The isolation and identification of the etiological agent of infectious hepatitis still defies elucidation. Gamma globulin is recommended for the provision of passive protection against hepatitis when such protection is indicated.

This session concluded with an address by Dr. F. C. Pace, Medical Consultant, Special Weapons Section, Emergency Health Services, Department of National Health and Welfare, on the subject of "The Role of the Physician in Disaster Planning". Dr. Pace pointed out that the fact that the medical and allied professions have already contributed materially in planning in the event of potential disasters may have become obscured by the fact that certain federal agencies act as co-ordinators and promulgators of principles developed by others. In a wide sense, the Emergency Measures Organization (formerly Civil Defence) performs these functions on behalf of the Privy Council. Professionally speaking, Emergency Health Services, a division of the Department of National Health and Welfare, has an analogous responsibility in the professional field. The roles of this federal health authority, in summary, are the provision of an administrative framework for disaster planning and operations, the co-ordination of provincial and municipal plans, the supply of medical materials for use in disaster, and the provision of information and education in disaster planning. The non-governmental health professions have made important contributions by providing responsible advice in working out disaster plans, in trials of such plans and in participation in actual disaster programs. Dr.

Pace presented a brief description of examples of a provincial and municipal disaster plan and emphasized the need for public health planning for such emergencies. He referred briefly to the subject of nuclear disasters and to the usefulness of local plans when integrated into the national effort. In this connection mention was made of the role of the Canadian Forces Medical Service and the potential usefulness of operational research. Throughout his address, Dr. Pace emphasized that the federal agencies at all times work through provincial organizations in all phases of disaster planning.

D.C.G.

(To be concluded)

## CANADIAN THORACIC SOCIETY

## Annual Meeting

Queen Elizabeth Hotel, Montreal

Tuesday, June 20, 1961

## PRELIMINARY PROGRAM

President: Dr. Roland Guy, Montreal.

9.00 a.m. Registration—Bersimis Room.

9.15 a.m. Address of Welcome and an outline of tuberculosis in the Province of Quebec.

10.00 - 11.30 Panel Discussion: "The Present-Day Treatment of Tuberculosis—Who Is Responsible?" Chairman: Dr. Gaetan Jarry, Medical Director, Bruchesi Institute, Montreal.

Reporting: Dr. Edward A. Allen, Division of Tuberculosis Prevention, Province of Ontario.

Drug Resistance: Dr. Paul Dionne, Bacteriologist, Sacred Heart Hospital, Montreal. What Is Adequate Treatment?: Dr. J. Earle Hiltz, Medical Superintendent, Nova Scotia Sanatorium, and Director of Tuberculosis Control, Province of Nova Scotia.

The Health Officer: Dr. Graham B. Lane, Director, Porcupine Health Unit, Ontario. The University and Teaching Physician's Views: Dr. Jonathan F. Meakins, Assistant Professor of Medicine, McGill University, Montreal.

The Place of Home Treatment: Dr. Fernand Moisan, Consultant to the Chest Clinic, Quebec City.

11.45 - 12.30 Guest Speaker: Professor Maurice Mayer, Paris, France: "The Treatment of Genital Tuberculosis in the Maternity Service of St. Antoine Hospital, Paris, France."

12.45 - 2.15 p.m. Luncheon and Annual General Meeting, Canadian Thoracic Society, Gatineau Room, Queen Elizabeth Hotel.

2.30 - 3.15 p.m. Dr. Robert H. Ebert, President-Elect, American Thoracic Society, Professor of Medicine, University Hospital of Cleveland, Ohio: "Fibrosis of the Lungs".

3.15 - 4.30 p.m. Panel Discussion: "Dyspnea—Its Causes and Treatment", Chairman: Dr. André MacKay, Director of the Chest Clinic, Notre Dame Hospital, Montreal.

Dr. Robert H. Ebert, President-Elect, American Thoracic Society.

Dr. Cecil G. Shaver, Medical Superintendent, Niagara Peninsula Sanatorium.

Dr. Colin R. Woolf, Research Associate, Ontario Heart Foundation.

Dr. André Proulx, Chief, Department of Cardiology, Sacred Heart Hospital, Montreal.

It is hoped that simultaneous interpretation into English or French, as required, will be available for the meeting.

Members wishing to make hotel reservations are requested to make these as soon as possible direct with the hotel of their choice, preferably on the form printed in recent issues of the *Canadian Medical Association Journal*.

## SOCIÉTÉ CANADIENNE DE THORACOLOGIE

## Réunion annuelle

Hôtel Reine Elizabeth, Montréal

Mardi, le 20 juin, 1961

## PROGRAMME PROVISOIRE

Président: Dr. Roland Guy, Montréal.

9.00 a.m. Inscription—Salon Bersimis.

9.15 a.m. Discours de bienvenue et coup d'oeil sur la Province de Québec au point de vue de la tuberculose.

10.00 - 11.30 Colloque: "Les méthodes modernes de traitement de la tuberculose—Qui en est responsable?" Président—Dr. Gaétan Jarry, Directeur Médical, Institut Bruchési, Montréal.

Inscription des tuberculeux: Dr. Edward A. Allen, Département de la Prévention de la tuberculose, Province d'Ontario.

Résistance bactérienne: Dr. Paul Dionne, Bactériologiste, Hôpital du Sacré-Cœur, Montréal.

"En quoi consiste un traitement adéquat?" Dr. J. Earle Hiltz, Surintendant médical, Sanatorium de la Nouvelle Ecosse et Directeur du Service de Prévention de la Tuberculose en Nouvelle Ecosse.

Le Médecin hygiéniste: Dr. Graham B. Lane, Directeur de l'Unité Sanitaire de Porcupine, Ontario.

L'Université et le Professeur de Médecine: Dr. Jonathan F. Meakins, Professeur-adjoint de médecine, Université McGill, Montréal. Le rôle du traitement à domicile: Dr. Fernand Moisan, Médecin consultant, Clinique Pulmonaire de la Ville de Québec.

11.45 - 12.30 Conférencier invité—M. le Professeur Maurice Mayer, Paris, France: "Le Traitement de la tuberculose génitale à la Maternité de l'Hôpital St-Antoine, à Paris."

12.45 - 2.15 p.m. Déjeuner et Réunion Annuelle, Société Canadienne de Thoracologie, Salon Gatineau, Hôtel Reine Elizabeth.

2.30 - 3.15 p.m. Dr. Robert H. Ebert, Futur président de la Société Américaine de Thoracologie, Professeur de Médecine à l'Hôpital Universitaire de Cleveland, Ohio: "La sclérose pulmonaire".

3.15 - 4.30 p.m. Colloque: "La dyspnée — causes et traitement". Président: Dr André MacKay, Directeur de la Clinique pulmonaire de l'Hôpital Notre-Dame de Montréal.  
Dr Robert H. Ebert, Futur Président de la Société Américaine de Thoracologie.  
Dr Cecil G. Shaver, Surintendant médical du "Niagara Peninsula Sanatorium".  
Dr Colin R. Woolf, Membre de la Commission des Recherches de la "Ontario Heart Foundation".

Dr André Proulx, Directeur du Service de Cardiologie, Hôpital du Sacré-Cœur, Montréal.

Les membres qui désirent réserver des chambres à l'hôtel sont priés de s'adresser au plus tôt directement à l'hôtel de leur choix, en utilisant si possible la formule annexée aux derniers numéros du *Journal de l'Association Médicale Canadienne*. La Société de Thoracologie et l'Association Antituberculeuse ne sont pas à même de réserver des chambres à cette occasion.

## GENERAL PRACTICE

### REPORT OF THE EXECUTIVE DIRECTOR\*

W. VICTOR JOHNSTON, M.D.



THE COLLEGE of General Practice of Canada was founded seven years ago. To the ancients, seven years was often referred to as the period of creation. The number seven had a symbolic meaning denoting completeness or perfection. What progress

has the College made in its seven years?

Establishment of the College was an educational approach to the problems of the general physician. There was to be maximum emphasis on standards and a minimum emphasis on politics. This interest in education involved a serious concern with training for general practice at the undergraduate level and internship level and with continuing instruction for the practising physician. It was also concerned with ways and means by which he can retain an honoured place on the medical staff of his neighbourhood general hospital, whether it be large or small.

Competence in any medical field in this modern world is built upon the quality of training received in preparation for it at both the undergraduate level and internship levels. In the undergraduate period the medical schools are concerned with training what they call the basic doctor. In the internship period, training is directed to more specific fields. In both of these areas we have to define carefully what general practice is, if we are to come up with serious suggestions for improved training and to participate actively in it.

In the training of a basic doctor the College believes that it is wrong for medical students to be exposed only to specialists in their undergraduate medical curriculum, and that there should be some instruction by senior general physicians. Medical educationalists hold the key to the future of general practice. What do they think of this con-

cept? Dean J. F. McCreary of the University of British Columbia will be supporting it in his address at this convention.

The University of Saskatchewan has appointed Dr. Sam Wolfe as a full-time Assistant Professor in the Department of Social and Preventive Medicine. Dr. Wolfe will have a major responsibility for developing programs of teaching and research in the area of general practice and family care. He comes to his new task after seven years of rural practice in Saskatchewan and three additional years in postgraduate studies, the last two of which have been spent as a Fellow of the Rockefeller Foundation at Columbia University.

There are no clearly defined directions at the present time for the establishment of such a Family Care Plan in a university setting. However, fortunately this appointment occurs in Saskatchewan where there are already excellent preceptorship programs conducted by senior general physicians in rural and more recently in urban centres. We know that our Saskatchewan Chapter and the Department of General Practice of the University of Saskatchewan will do all in their power to co-operate with Dr. Wolfe in the definition and attainment of common objectives, so that mutually acceptable programs in family care and general practice teaching can be developed. Any proposals for a Family Care Plan should be critically and constructively examined to expose deficiencies and not to overlook possibilities that may contain the seeds of a better academic status for general practice.

Professor Stanley Greenhill of the Department of Social and Preventive Medicine of the University of Alberta has worked out a Family Care Plan for that medical school. It is awaiting implementation.

I submit that these are significant developments in the rapid scientific progress of what I might choose to call our specialty of general practice. A number of our leaders have asked this question: Should not the College be thinking seriously of raising funds to be applied to a demonstration of the very best that general practice can do in a university medical school?

\*Presented at the National Scientific Assembly, The College of General Practice of Canada, Vancouver, March 1961.

At the internship level we have, of course, a program of General Practice Residencies. In this particular field, I would like to draw attention to a forward-looking realistic conference held last August in Sydney, Australia. At this conference, Australian general practitioners discussed what was to be the immediate postgraduate education for a doctor who was electing to enter general practice. Its theme was "Training in the First Five Postgraduate Years". A report of their conclusions is given in the March 1961 issue of the *Bulletin* of this College. You will find it fascinating reading. Perhaps we should have a similar national conference of general physicians in Canada. Certainly the importance of this subject would justify such an approach.

Instruction for practising family doctors constitutes one of the most important activities of the College. Millions of dollars are spent annually on medical research, with a resulting stream of wonderful new discoveries. We must ensure that the fruits of this knowledge get through to the practising doctor. To meet this need there has been a remarkable expansion, under College encouragement, of clinical days, study courses, etc., but in no part of Canada have we yet approached the saturation point.

Our lending library of medical tape recordings has become well established during the past year. Members of the College have all received a copy of its first attractive catalogue. The initial program of two- and three-week concentrated study courses in certain hospitals at a time and on subjects of the doctor's own choosing helps to fill other specific educational needs of our members.

The questionnaire to all College members on our "Fellowship Plan" has proved to be a major task of soul-searching. This is an attempt to evaluate the virtues of a form of specific recognition for high achievement in general practice. It is part of a study of how best to build a career structure for general physicians comparable to what has been done in other medical fields.

There has been a marked increase in the number of Canadian hospitals with Departments of General Practice. There are now nine Canadian university teaching hospitals developing such departments. More and more large general hospitals are doing the same. These departments are undertaking responsible tasks of considerable diversity. For instance, some are staffing their outpatient departments. Many have their own high-quality clinical meetings, and one in Edmonton is instituting its own ward rounds. Our Committee on Hospitals has undertaken an analytical study of this situation through a questionnaire to nearly all general hospitals in Canada. This should provide very valuable information to guide us in any further expansion of this program.

Our Research Committee is rapidly extending its work. It has been greatly encouraged by the fact that general physicians, both individually and collectively, are coming forward with constructive research proposals.

I have emphasized the many facets of the College's educational approach to the general practice of medicine because of their importance to the

entire climate of general practice. They are based on the premise that general practice can best become a dynamic force through emphasis on competence. This is also the best approach for asserting the general practitioners' rights for full participation in hospital medical staff activities. Moreover, training in this field is now at the bar of medical educationalists' opinion.

To attain these objectives the College provides a concrete form of binding force for general physicians at all levels—national, provincial and local. It provides for a group effort to achieve its goals. It is built around a hard core of practitioners who see the value of further continuous education and who realize that we can never stand erect so long as we are at all dependent upon the incompetent. This is no mere negative virtue. It is based on the hard fact that every improvement—every reform, if you will—is dependent upon the fitness of the men who carry it out. It is prudent insurance against submergence.

Both social medicine, or the broad social value of good family practice, and preventive medicine are important elements of general practice, but don't let us over-magnify them, as they are not general practice *per se*. A good family physician must know a lot about modern medicine, and the more complex medicine becomes, the greater become the reasons why the public should have personal physicians to keep medicine in its proper perspective for them. So great is this need that if the family doctor should disappear tomorrow, he would again have to be invented. This area of medical care—that is, of applying the modern techniques of diagnosis and treatment to particular people at all hours of the day or night and with full understanding of them, their homes, and working conditions—is an area that we can legitimately carve out as our own. It constitutes a special task.

In summary, after seven years' experience, the College continues to appreciate that its greatest needs are two in number. First, a rapid scientific development of general practice, because the family doctor must be the very best doctor in his field. Secondly, the maximum College membership possible within the limits imposed by our standards. We can do collectively so much more than we can ever do individually.

Our progress has been very substantial. Financial support from the College membership through large donations to the Sustaining Fund, and the gratifying increase in membership during the past year, are proofs of your desire to give us the tools to carry these tasks to completion. It is most gratifying to us that we are developing so many able leaders so quickly.

If we wish to be big, we must think big and act big. And bigness here is not used so much in the sense of numbers, but rather in prestige and importance. In this way the modern family doctor can hold his place in the heart of medicine as the oldest and latest specialty.

To our members I would say that we hope your membership in the College of General Practice will be a source of strength to you. Trust and assist it, and I believe it will not fail you. Personally, it has been most stimulating to work with you all.

## ASSOCIATION NOTES

### THE NINETY-FOURTH ANNUAL MEETING: PROTOCOLS OF CASES TO BE DISCUSSED AT THE CLINICO-PATHOLOGICAL CONFERENCE, JUNE 22

*The two case summaries reproduced below will be the subjects of discussion at a Clinico-Pathological Conference which will be held on Thursday, June 22, during the Association's Annual Meeting. Dr. Douglas G. Cameron, Montreal, will be Chairman of the Conference and the other participants will be: Dr. Gardner C. McMillan, Montreal, and Dr. Carlton Auger, Quebec City, pathologists; Dr. C. C. Gray, Toronto, Dr. R. C. Dickson, Halifax, Dr. John Kilgour, Winnipeg, and Dr. John Howlett, Montreal, clinicians.*

*Members of the Association who are planning to attend the Annual Meeting are invited to study these protocols at their leisure at home, to provide added interest in their discussion at the Clinico-Pathological Conference and to derive the maximum instructional benefit from this session.*

Les textes français de ces protocoles de cas seront publiés dans la parution du 10 juin.

#### CASE 1

A 64-YEAR-OLD white man developed a rash on his left leg following trauma in October 1960. The rash failed to clear completely and three months later it spread to the trunk and other limbs.

#### FIRST ADMISSION

On January 4, 1961, he was admitted to hospital complaining of the itchy skin eruption. The only previous illness of note was gout which began in his great toe three years before and later involved his left knee. This condition was treated with colchicine alone for two years and with colchicine and phenylbutazone (Butazolidin) during the third year. Both agents were discontinued three weeks before admission. His mother died of asthma at 56 years and his father of cancer at 71. One brother died of high blood pressure.

The patient's temperature was 99.4° F., pulse 70, and blood pressure 150/95 mm. Hg. The rash was noted to involve all limbs and the front of the trunk. It was maculopapular, confluent and did not weep. The lungs were clear and the heart was normal. His weight was steady at 195 lb. The joints were not deformed, but there was a trace of pretibial edema. Urine specific gravity ranged up to 1.017, and one sample taken while the patient was febrile contained a trace of protein, and 5-8 red blood cells per high-power field. The blood urea nitrogen (BUN) value was 21 mg. %. The dermatitis subsided slowly on starch baths, milk and water compresses. On the third hospital day he developed acute gout in his right big toe which

responded promptly to administration of ACTH and probenecid (Benemid). Maintenance doses of colchicine and probenecid were prescribed and the patient was sent home on January 21 free of symptoms.

#### SECOND ADMISSION

He was re-admitted on February 22, 1961, because of severe dyspnea, edema and oliguria. He had been well until two weeks before admission when he developed a sore throat and cough with scanty sputum, occasionally blood-streaked. The urine decreased in amount and became "tea-coloured". He had anorexia and mild diarrhea. Colchicine and probenecid were discontinued. Ten days before admission, edema, puffiness of the eyes and headache appeared. At the time of admission dyspnea was severe and he had gained 15 lb. in weight.

On examination, his temperature was 100° F., pulse 108, respirations 28, and blood pressure 130/80. He was in respiratory distress but there was no cyanosis. The pharynx was diffusely red. The pulse was regular, the heart was not enlarged, the sounds were clear, but a gallop rhythm was heard. There was dullness to percussion at the lung bases and moist rales were heard throughout both lung fields. There was pitting edema of the ankles but no jugular venous engorgement. The skin was clear. Twitching movements of the extremities, lethargic speech and drowsiness were noted. Urine passed at this time was deeply coloured and contained 300 mg. % protein; microscopic examination was not done. Non-protein nitrogen value was 70 mg. %.

The clinical picture of uremia prompted his transfer to The Montreal General Hospital on February 25, 1961.

#### THIRD ADMISSION

The clinical picture was much the same. His temperature was 99.6° F., pulse 100, respiratory rate 26, and blood pressure 150/85. He weighed 203 lb. There were no retinal hemorrhages and no papilledema, but a patch of retinal exudate was seen. Moist rales were heard at the lung bases and signs of bilateral pleural effusion were noted. There was shifting dullness in the abdomen.

Urine obtained on admission (an insufficient amount for determination of the specific gravity) was "coffee-coloured" and contained 300 mg. % protein and gross numbers of red cells, as well as hyaline, granular and red cell casts. Results of determination of serum values on admission showed BUN 69 mg. %, chloride 89 mEq./l., bicarbonate 21 mEq./l., sodium 118 mEq./l., and potassium

6.7 mEq./l. The blood picture was as follows: Hb 10.7 g., hematocrit 33%, sedimentation rate 33 mm. in one hour, reticulocytes 1%, white cell count 12,100, with 86% polymorphonuclear leukocytes, 4% lymphocytes and 6% monocytes. An electrocardiogram showed sinus tachycardia. A chest roentgenogram revealed small bilateral pleural effusions, pulmonary congestion, and a heart shadow within normal limits. A plain film of the abdomen showed normal kidney outlines but no opacity suggesting stones.

An inferior vena cava catheter was introduced and fluid intake was restricted to 400 c.c. per day together with an amount equivalent to the daily urine output. The daily weight was recorded, he was digitalized, exchange resins were administered and he was given anabolic hormone therapy. During the first eight days his urine output varied from 50 to 300 c.c. per 24 hours. His weight dropped to 194 lb., his level of consciousness brightened, and the muscular twitching decreased. The potassium level dropped to 4.7 mEq./l., but the BUN climbed to 150 mg. %. He was nauseated but did not vomit and there was no troublesome diarrhea.

Bacteriological studies showed a heavy growth of *Staphylococcus pyogenes* from the throat. A renal biopsy was performed on the 5th hospital day and cultures of the biopsy material were sterile. Antistreptolysin "O" titre was 168 units. Urine passed on the 6th hospital day contained 33 mEq./l. of sodium and 44 mEq./l. of potassium, and had an osmolarity of 352 m.osm./l. Repeated microscopic examinations of the urine showed the same features noted in the initial specimen.

During the last six days of his life the patient remained oliguric (urine output 0-200 c.c. per 24 hours). His general condition remained the same. With rigid fluid and electrolyte management his weight continued to decline by 1 to 2 lb. per day. On March 11 he developed watery diarrhea and became somnolent. Results of blood chemistry studies on that day showed a BUN value of 198 mg. %, bicarbonate of 21 mEq./l. and potassium of 4.4 mEq./l. A decision was made to dialyze the patient the next morning.

After periods of agitation and hypotension during the night of March 11, the patient gasped and died suddenly in the early hours of March 12, 1961.

## CASE 2

A WHITE WOMAN, aged 63 years, developed shortness of breath on exertion and vague precordial pain in 1954, and swelling of the legs in 1956. In June 1956, she was found to have fluid in her right chest, for which a thoracentesis was performed. She had had a poor appetite and had lost a considerable amount of weight, strength and colour. The leg swelling was controlled fairly well by treatment at home. She had recently noted that she bruised easily after minor trauma.

## FIRST ADMISSION

On October 8, 1956, she was admitted to the Royal Victoria Hospital complaining of nausea, vomiting, diarrhea, weakness, dizziness and burning on micturition of four days' duration. She gave a history of amputation of the left foot for injury at 12 years, perforative appendicitis at 16, herniotomy at 31 years, and four normal pregnancies, but otherwise no ill health till the onset of the present illness. Her father and mother had died at 56 and 65 years respectively, of coronary disease. Her husband died of coronary disease in 1950.

On examination she showed evidence of weight loss but was in no acute distress. Temperature was normal, heart rate 90 per minute and blood pressure 135/105 (subsequently 110/70). She weighed 123 lb. The fundi were considered normal for her age. The right lobe of the thyroid was noted to be enlarged, smooth and non-tender. There were dullness and diminished breath sounds at the right lung base, a soft apical systolic murmur, right costovertebral and right upper quadrant tenderness, a left midtarsal amputation and no other signs of note.

The urine specific gravity was 1.022. It was free of albumin and contained 20-30 red blood cells and 10-15 white blood cells per high-power field. Culture yielded a moderate growth of *Alcaligenes faecalis*. Cystoscopy disclosed an inflamed bladder mucosa, clear urine from both ureters, normal pyelograms and questionable evidence of external pressure on the right ureter. The hemoglobin value was 96%, hematocrit 45%, and sedimentation rate 11 mm. in one hour. The total white cell count was 10,200, with slight neutrophilia. Clotting factors were normal. A chest roentgenogram and fluoroscopy showed densities in the lower parts of both pleural spaces consistent with moderate right and small left effusions or pleural thickening, obscuring the heart borders; the heart was difficult to define. Findings on barium enema examination were normal.

She was treated with digitalis, dimenhydrinate (Dramamine) (for nausea), sulfoxazole and nitrofurantoin (Furadantin) successively for urinary tract infection. It was noted that she bled excessively from the bladder after cystoscopy and still showed microscopic hematuria at time of discharge on October 27, 1956.

## SECOND ADMISSION

She was re-admitted on October 30, 1956, because of gross hematuria with clots observed the day after discharge, and vomiting of 24 hours' duration. She was flushed and looked chronically ill but had no fever. The physical signs were the same as on the previous admission, except that the eyes were noted to be somewhat prominent and staring; the blood pressure was 90/60; and the liver edge was palpable, smooth and slightly tender one

fingerbreadth below the right costal margin. Pelvic examination and cervical cytology were negative. The urine specific gravity was 1.023 with 1 plus albumin, many red blood cells and a few white blood cells per high-power field and no casts. Hemoglobin value was 86%, hematocrit 41, and sedimentation rate 21. The white blood cell count was 5400. Platelet count and bleeding, clotting and prothrombin times were normal. The bone marrow showed some generalized hyperplasia, consistent with recent blood loss. She underwent cystoscopy three times because of recurrent bleeding from the bladder. On one occasion two ulcerated areas on the posterior wall were coagulated. A biopsy showed inflammatory tissue. The third cystoscopy showed many areas of submucosal hemorrhage, interpreted as interstitial cystitis. Retrograde pyelograms were normal. Urine culture grew coliform bacteria and anaerobic streptococci. Treatment included administration of sulfonamides, nitrofurantoin (Furadantin), tetracycline and oleandomycin. Gross hematuria cleared within three weeks, but microscopic hematuria was again present at the time of discharge on December 2, 1956. Her blood pressure had averaged 120/70 and her weight had dropped from 121 lb. to 115 lb.

#### THIRD ADMISSION

She was re-admitted on March 2, 1957, for control of peripheral edema and shortness of breath which had returned gradually and had become refractory to digitalis, mercurials and acetazolamide (Diamox). She required two pillows at night and her weight had increased 30 lb. to 145 lb. She was dyspneic at rest. There were numerous ecchymoses scattered over her body and a right scleral hemorrhage was noted. Blood pressure was 140/90 and pulse rate 70, with numerous extrasystoles. The thyroid showed nodular enlargement of both lobes which were hard. Moist rales were heard in both lung bases, with dullness at the right base. Marked edema of the lower abdominal wall, sacrum and legs was present.

The urine showed a trace of albumin but was otherwise negative. Non-protein nitrogen value was 31 mg. %, total protein 5.32 g. %, albumin 4.15 g. %, globulin 1.17 g. %, cholesterol 200 mg. %, protein-bound iodine 6.5,  $I^{131}$  uptake 10.2% in 24 hours. Electrolyte determinations showed a low chloride value on admission, later rising to normal, and normal sodium and potassium values on three occasions.

#### FOURTH ADMISSION

She was re-admitted on September 29, 1957. She had seemed fairly well until July 1957 when edema of the legs reappeared and failed to respond to digitalis and diuretics and her weight rose 13 lb. When re-admitted she complained of edema of her legs, anorexia, drowsiness, nocturia (x 2), increased urgency, and easy bruising and bleeding.

She was afebrile and looked thin, but had marked edema of the legs. Both lobes of the thyroid were grossly enlarged and firm. The blood pressure was 115/80 and pulse rate 96 and regular. Dullness and diminished breath sounds were present at the right base. The external jugular veins were distended, the right more than the left. The liver edge was palpable three fingerbreadths below the right costal margin. Ecchymotic areas were noted on the anterior chest wall and a brownish discoloration over the sacrum. The Rumpel-Leede test was positive.

The urine specific gravity was 1.010 with 2 plus albumin; there were a few more white blood cells than normal per high-power field, 0-24 red blood cells and tubular and granular casts. Urine culture grew *E. coli communior* and streptococcus species. The hemoglobin was 99%, hematocrit 51%, sedimentation rate 13 mm. in one hour, and white cell count 8800, with a normal differential count. The platelet count and bleeding, clotting and prothrombin times were normal. The electrophoretic pattern showed an elevation of alpha-2 globulin. The chloride level was 94 mEq./l., sodium 134 and potassium 6.2. A chest roentgenogram (October 2) showed cardiac enlargement, difficult to define, moderate pulmonary congestion and right pleural effusion. The electrocardiogram showed sinus rhythm, normal conduction, absent Q and notched R waves in V5 and 6 indicating left bundle branch block, and digitalis-type ST-T complexes in AVF, lead 3, V5 and V6. Treatment was continued with low salt diet, digitalis and occasional injections of mercurials. Improvement was transient and followed by progressive weight gain. The hemorrhagic manifestations persisted; there were ecchymotic areas and hematoma related to pressure and minor trauma but no petechial or small purpuric lesions. Gross hematuria was noted 10 days after admission, and cleared spontaneously in four days. Chlorothiazide was given without any effect on the edema. On November 8, prednisone therapy was commenced, with slight initial diuresis. On November 11 she vomited several times and complained of yellow streaks of light in her vision. That evening she developed severe epigastric pain and dyspnea and was observed to have a "poor colour". On November 12, dyspnea was greater and there were many rales at the lung bases. Her pulse rate was 84, with occasional extrasystoles, and blood pressure was 110/60. She became very anxious but slept well that night. On November 13, at 6.30 a.m. she called for a bedpan and a few minutes later was found dead in bed.

## ANNUAL MEETING NEWS

## SCIENTIFIC EXHIBITS

Visiting doctors will find much of interest awaiting them when they visit the scientific exhibits on the Convention Floor of the Queen Elizabeth Hotel, Montreal, June 19-23.

These exhibits are of an educational nature and represent many affiliated medical and lay societies. In addition, some of the display arrangements will feature reports on scientific research projects by C.M.A. members across Canada.

## MEDICAL EXHIBITS

Through the co-operation of the Medical Exhibitors Association of Canada, some ninety colourful exhibits will be displayed this year on the Convention Floor of the Queen Elizabeth Hotel.

These exhibits include pharmaceutical, medical and surgical equipment; food products, and medical books. They represent the leaders in their respective fields, and their products symbolize developments in keeping with the scientific advancement of Canadian medicine. Pay them a visit! You will meet old friends and new products.

## DOCTORS AND ART

The Quebec Division of the Canadian Medical Association, in conjunction with the Montreal Museum of Fine Arts, is sponsoring an exhibition of painting and sculpture collected by some of the doctors in the Montreal area. The exhibition is being held at the Museum, 1379 Sherbrooke Street West, from June 6 to June 30. It is hoped that all doctors and their wives will visit the show. The Museum is open daily from 10 a.m. to 5 p.m.

The collection comprises approximately 150 original sculptures and paintings which have been lent by 50 doctors in the Montreal area. They contain some notable work by artists such as Dufy, Utrillo, Renoir, Kreighoff and Modigliani; and sculptures of Henry Moore, Epstein and Gord. Members and their wives attending the meeting will be well rewarded by a visit to the Museum. Admission is free.

MEMORIAL SERVICE FOR  
DR. WILLIAM V. CONE

On Sunday morning, June 25, a memorial window in memory of the late Dr. William V. Cone will be dedicated at St. Andrew's United Church, 101 Côte St. Antoine, Westmount.

The address will be given by Dr. Wilder Penfield. The President of the Canadian Medical Association, and other prominent members of the medical profession, will participate in this memorial service.

MONTREAL GENERAL HOSPITAL  
"ALUMNI AT HOME"

The Montreal General Hospital announces that an At Home for members of the medical and dental professions who have been associated with the hospital on the intern or attending staff will be held immediately after the C.M.A. meeting.



Canadian Government Travel Bureau, Ottawa  
Montreal—from the lookout atop Mount Royal.

The At Home program will comprise a dinner at the Queen Elizabeth Hotel on Friday, June 23, and a wide variety of functions at the hospital on Saturday morning, June 24, including selected operations, demonstrations in the new surgical and medical research laboratories, clinical demonstrations in the dental department, tours of the hospital and an informal reception in Livingstone Hall concluding at noon.

Dr. S. A. MacDonald, Chairman of the At Home Committee, informs the Journal that the dates and the program have been selected to complement but not duplicate or interfere with Canadian Medical Association sessions, and to enable all M.G.H. Alumni attending the C.M.A. meeting to renew acquaintances with their fellow graduates as well as to observe the tremendous recent developments in the hospital, and that the C.M.A. graciously extends an invitation to M.G.H. Alumni who are not C.M.A. members to attend the technical and social sessions of its annual meetings which conclude on the afternoon of Friday, June 23.

Alumni At Home registration desks will be set up in the Queen Elizabeth Hotel and at the hospital during the C.M.A. meeting where those who wish to participate may obtain full information and register for all or part of the At Home program.

MEETING OF THE CANADIAN  
OPHTHALMOLOGICAL SOCIETY,  
QUEEN ELIZABETH HOTEL,  
MONTREAL, JUNE 11-14, 1961

Council Meeting will be on June 11 starting at 10 a.m.

The Scientific Sessions will take place on the mornings of June 12, 13 and 14. These cover a wide range of general ophthalmological subjects and the program is a very full one.

The afternoon of June 12 will be occupied by papers on research in ophthalmology.

The Annual Business Meeting of the Society will take place on the afternoon of June 13, starting at 2.15 p.m.

The noted neuro-ophthalmologist, Dr. Frank Walsh of Baltimore, will be guest of honour and will address the Scientific Sessions on two occasions.

CONNAUGHT

# IMMUNE SERUM GLOBULIN (HUMAN)

The production of Immune Serum Globulin (Human) by the Connaught Medical Research Laboratories has been made possible by the cooperation of the Canadian Red Cross Society, the Federal Government and the Governments of each of the Provinces.

Immune Serum Globulin is distributed by Provincial Departments of Health and also by the Canadian Red Cross Society through its regional blood depots for therapeutic purposes only. In addition, Immune Serum Globulin (Human) prepared from blood collected privately is available directly from the Laboratories on a regular sale basis.

Some of the conditions for which Immune Serum Globulin is indicated are:

- |                          |   |
|--------------------------|---|
| Measles (rubeola)        | —For prevention and modification.                   |
| Hypogammaglobulinæmia    | —For maintenance of the patient's resistance to     |
| and                      | infection.  |
| Agammaglobulinæmia       |   |
| Infectious Hepatitis     | —For close contacts or in the control of outbreaks. |
| Poliomyelitis            | —For prevention and modification.                   |
| German Measles (rubella) | —For prevention during early pregnancy.             |



CONNAUGHT MEDICAL RESEARCH LABORATORIES  
UNIVERSITY OF TORONTO  
TORONTO 4, CANADA

*Established in 1914 for Public Service through  
Medical Research and the development of  
Products for Prevention or Treatment of Disease.*

## BOOK REVIEWS

**FETAL ELECTROCARDIOGRAPHY.** The Electrical Activity of the Fetal Heart. American Lecture Series. Saul David Larks. 108 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1961. \$7.25.

In recent years increasing attention has been paid by both obstetricians and pediatricians to fetal physiology in an attempt to gain a better understanding of clinical conditions which are determined prenatally. The fetal electrocardiogram has been one of the research tools employed, and this little volume summarizes the state of development of this technique at the time of publication.

The introductory chapters deal briefly with the historical, biophysical and technical aspects of fetal electrocardiography, and the later chapters are devoted to a description of its use in normal and abnormal states. The limited value of the technique is apparent even to one not involved in the field of obstetrics, and its advantages have perhaps been overemphasized while its limitations have not been stressed sufficiently by the author. He notes that a negative fetal electrocardiogram does not have much meaning, yet cites examples of the usefulness of negative tracings in supporting a clinical diagnosis of fetal death or molar pregnancy. He suggests that congenital heart block can be diagnosed *in utero* when in fact the fetal P waves are not shown and all that the electrocardiogram records is bradycardia, a sign detectable on auscultation. Changes in the fetal heart rate under circumstances producing distress are mentioned, but the author omits any discussion of the value of electrocardiography in predicting fetal death, surely one of the most important potential values of the technique.

The few examples given of morphological changes in the fetal complexes reflecting abnormal fetal physiology hint at the promise of this technique when it is developed to the stage that the individual complexes will be capable of detailed analysis. The problems involved in refining techniques to this extent are unfortunately not discussed.

This monograph indicates clearly the value of fetal electrocardiography in research on both man and animals and was appropriately written by a researcher rather than a clinician. It should prove a useful stimulus to further work in this field.

**CONTRIBUTIONS TO OBSTETRICS AND GYNECOLOGY.** V. N. Shirodkar. 158 pp. Illust. E. & S. Livingstone Ltd., Edinburgh; The Macmillan Company of Canada Limited, Toronto, 1960. \$6.35.

It has always been a firm principle that in order to prevent potatoes falling out of a sack, a string is tied around the neck. This principle is even more important if the sack happens to be upside down. Shirodkar's operation for suture of the incompetent cervical os to prevent second-trimester miscarriage embodies this principle and by its simplicity represents a great medical advance.

The chapter describing this operation forms the core of this book. It is magnificently illustrated with unusually clear photographs which demonstrate the fine details of this operation.

The second chapter dealing with the problem of prolapse describes an extended form of the Manchester operation dispensing with amputation of the cervix and utilizing the uterosacral ligaments for support. This maintains the maximum reproductive performance of the young woman with symptomatic prolapse, a condition apparently fairly frequently encountered in India.

Illustrating the author's capacity for inventing new instruments, the chapter on the surgery of blocked tubes is an excellent and well-illustrated description of his tubal implantation procedure. One may speculate that, properly applied, these three operations will bring many pregnancies to fruition, a strange advance from the land of the "population explosion".

This brings us up to page 84. These three chapters are extremely valuable for the specialist gynecologist and are highly recommended. It is this reviewer's opinion that the book should stop here. It is almost complete if the title is taken literally.

There follows an extremely complicated operation for the construction of an artificial vagina which is not original and for many years has been superseded.

The rest of the book is said to consist of summaries of various papers by the author. They are supposed to be written for "young and old alike". They are really a mixture of rather obvious hints for beginners interspersed freely with diagnostic vignettes in which the author nearly always comes off best.

With these reservations, this book is highly recommended for the practising gynecologist.

**ANAESTHETIC ACCIDENTS.** The Complications of General and Regional Anaesthesia. 2nd ed. V. Keating. 282 pp. Illust. Year Book Publishers, Inc., Chicago, Ill., 1961. \$5.50.

In our present state of knowledge of anesthesia, one is faced with a choice of multiple agents and techniques. In order to master each agent and each technique one must be well versed in the dangers and pitfalls related thereto. With knowledge of potential difficulties, many serious complications can be avoided before they develop. In this edition the author presents a very comprehensive review of the common and uncommon accidents related to anesthesia.

Dr. Keating approaches the various sections into which his subject matter is divided with a preliminary discussion of anatomy, physiology or pharmacology. In this manner each system or technique is concisely reviewed under the headings: The Circulation Under Anesthesia; Myocardium and Conduction system; Blood Supply; Autonomic Control; Peripheral Vascular Disturbances during Anesthesia; Blood Volume Reduction during Operation; Blood Pressure Disturbances; Pulse Rate Disturbances; Effects of Anesthesia on the Myocardium; Cardiac Arrhythmias under Anesthesia; and Heart Failure from Myocardial Disease during Anesthesia. Where more detailed information is desired, a large reference list may be consulted at the end of each section.

The book is recommended for all who are interested in anesthesia and especially for residents, to further their insight in the study of this specialty.

**WANTED.—LOCUM TENENS** for period of June, July and August 1961 or period thereof for practice 50 miles from Toronto. Salary \$700-\$800 per month depending on qualifications. Excellent swimming, boating and fishing area. Reply to Box 428, CMA Journal, 150 St. George St., Toronto 5, Ont.

**ALBERTA GENERAL PRACTICE.**—Eight-man group desire an assistant for active general practice in a large Alberta city. Applicant should have at least two years' approved internship. Please state age, marital status, training, and date available to Box 475, CMA Journal, 150 St. George St., Toronto 5, Ont.

**LOCUM TENENS IN DIAGNOSTIC RADIOLOGY** wanted to serve three hospitals in eastern Saskatchewan for August, September and October. Reply to Dr. L. Bakos, Yorkton, Saskatchewan.

**MEDICAL OFFICER OF HEALTH** required for Peace River Health Unit, on or after July 1. Further details and application forms from Mr. E. E. Taylor, Secretary-Treasurer, Box 84, Peace River, Alberta.

**LOCUM TENENS WANTED** for pleasant general practice, compact town in central Nfld., on TCH, from June 22 to September 5, or substantial part thereof. Car and house provided. Salary \$650 per month. Reply to Box 476, CMA Journal, 150 St. George St., Toronto 5, Ont.

**ASSISTANT PATHOLOGIST** is immediately required in a northern Ontario city. Future partnership option. Reply stating experience, salary desired and the names of two references. Reply to Box 477, CMA Journal, 150 St. George St., Toronto 5, Ont.

**WANTED.**—Trained ophthalmologist to be associated in hospital group of board eligible physicians and surgeons. Work largely on fee-for-service basis. Apply: Dr. J. M. Emmett, Chesapeake and Ohio Hospital, Clifton Forge, Virginia, U.S.A.

**DIAGNOSTIC RADIOLOGIST.**—Western Canadian group requires diagnostic radiologist either certified or certification eligible. First year salary leading to partnership. Canadian graduate. Reply giving full particulars to Box 464, CMA Journal, 150 St. George St., Toronto 5, Ont.

**WANTED.**—Trained otolaryngologist to be associated in hospital group of board eligible physicians and surgeons. Work largely on fee-for-service basis. Apply Dr. J. M. Emmett, Chesapeake and Ohio Hospital, Clifton Forge, Virginia, U.S.A.

**ASSISTANT WANTED** in general practice for July and August. Salary \$600 per month. New open hospital. Apply with references to Dr. C. E. Bodkin or Dr. J. G. Quarry, 490 Brant, Burlington, Ontario.

**LOCUMS REQUIRED**, group practice, northern Ontario. Three to five months starting in June or July. \$750 per month. Reply to Box 465, CMA Journal, 150 St. George St., Toronto 5, Ont.

**GENERAL PRACTITIONER REQUIRED** for the Village of Rocanville and district, equipped medical centre, house available. Apply to Fren Henderson, Sec.-Treas., Village of Rocanville, Saskatchewan.

**WANTED.—MEDICAL DOCTOR** for private practice in rural community in northwest Saskatchewan. New 10-bed hospital with x-ray, laboratory and excellent nursing staff. Population of hospital area, approximately 2000. Fully modern doctor's residence and new office facilities provided without charge. No other doctor in the community. Position available at once. For full particulars apply to Mr. W. F. Kuffert, Chairman, Rabbit Lake Union Hospital, Rabbit Lake Saskatchewan.

## Practices

**NOTE:** To avoid the publication of misleading information, all advertisers under the classification "Practices" in the Canadian Medical Association Journal should furnish the following information:

Population of community and surrounding territory served.

Number of doctors now practising in the community.

Location of nearest doctor if the community has no resident physician.

Location of nearest hospital.

Description and suggested price of premises for office and residence.

Whether or not an introduction of at least two months' duration may be afforded a prospective purchaser.

**PRACTICE WITH HOUSE FOR SALE** in a large southern Ontario town. Beautiful location. Excellent hospital facilities. Introduction if desired, terms can be arranged. Owner specializing. Reply to Box 770, CMA Journal, 150 St. George St., Toronto 5, Ont.

**GENERAL PRACTICE** in small town in eastern Ontario available by June 1961. Gross income \$20,000 per year. Accredited hospital, 15 miles away over first class roads. Reply to Box 459, CMA Journal, 150 St. George St., Toronto 5, Ont.

**FOR SALE.**—Established general practice, southern Ontario village. Good income, pleasant living and recreational area. Attractive home and office. Terms to suit purchaser. Small downpayment and low price to facilitate immediate sale. Specializing. Reply to Box 466, CMA Journal, 150 St. George St., Toronto 5, Ont.

**WELL-ESTABLISHED**, unopposed general practice for sale in eastern Saskatchewan. Gross income over \$25,000 from practice and \$22,000 from small drug store associated. 16-bed hospital in town, good schools. No real estate to buy. Asking less than 25% of one year's gross to cover equipment and drug stock. Will accept downpayment, and terms available on balance. Apply to Box 467, CMA Journal, 150 St. George St., Toronto 5, Ont.

**GENERAL PRACTICE.**—Established 30-years in thriving community, including obstetrics and pediatrics. Gross over \$35,000. Available in 3 months. 20 miles from teaching centre with open hospitals. House with fully-equipped office. Easy terms and with introduction. Weekend coverage can be arranged. Reply to Box 478, CMA Journal, 150 St. George St., Toronto 5, Ont.

**UNOPPOSED ESTABLISHED GENERAL PRACTICE** serving central New Brunswick famed Miramichi hunting and fishing area available immediately. Population about 3000. New modern 3-bedroom home with 4-room office suite attached, available at reasonable rental. Situated in Boiestown 40 miles from Fredericton on main highway. Small hospital within 20 miles. Apply P. D. Griffin, Miramichi Board of Trade, Boiestown, N.B.

## Residencies and Internships

**OPENINGS FOR SEVERAL HOUSE OFFICERS** in three hospital combined program. Two private hospitals, one brand new charity hospital. Approved one year rotating internship, approved two year general practice residency, several specialty residencies. Stipend \$400 for interns, \$425 for residents, exclusive of meals or maintenance. Appointment July 1. Apply Director of Medical Education, 609 Brent Annex, or phone HE. 8-8581, Pensacola, Fla., U.S.A.

**IOWA CITY.—PSYCHIATRIC RESIDENCIES:** Department of psychiatry, University of Iowa Medical Center; 3-year approved training; broad experience with adults and children, community services, inpatient and outpatient training and all types of psychiatric therapy under close supervision; master of science program for residents interested in academic and research careers; salary levels \$4000 to \$4500, also available package plan covering 5 years with periods of rotation in the Department of Psychiatry and the state mental hospitals and schools for mentally defective; salary levels \$7350 to \$13,200. For information and application blanks write: Paul E. Huston, M.D., Chairman, Department of Psychiatry, 500 Newton Road, Iowa City, Iowa.

**ROTATING INTERNSHIPS FOR 1961-62** for fully accredited 186-bed hospital with active teaching program. Approved by A.M.A. located near New York City. E.C.F.M.G. certification required. Stipend—\$250 a month, plus room and board. Travel allowance \$300. Write, Director of Medical Education, The Griffin Hospital, Derby, Connecticut, U.S.A.

**12-MONTH ROTATING INTERNSHIPS AND APPROVED RESIDENCIES** in pathology, pediatrics, surgery and obstetrics-gynecology. 350-bed, 65 bassinets general hospital with a large outpatient clinic. Located in midwest U.S. in the Great Lakes region. Medical education director. Well co-ordinated comprehensive program. Stipend \$275 per month, \$500 relocation bonus, \$67.50 food allowance per month, \$80 per month housing allowance for married interns, room furnished in interns' quarters for single interns, uniforms and laundry. Address inquiries to Director of Medical Education, Mercy Hospital, Toledo, Ohio, U.S.A.

**U.S.A., ST. LUKE'S HOSPITAL**, Newburgh, New York. (On Hudson River, 60 miles north of New York City, population 35,000). Rotating internships, approved by the American Medical Association. Very active general hospital, 247 beds (currently expanding to 310 beds). Full educational training program. Stipend \$250 per month with full maintenance. E.C.F.M.G. certification required. Apply to Director of Medical Education, St. Luke's Hospital, Newburgh, New York, U.S.A.

**RADIOLOGY RESIDENCY AVAILABLE.**—708-bed general hospital, midwest. Complete resident training for American board of radiology. Large new department including therapy and isotope divisions. Complete teaching facilities; staffed with board certified radiologists and six residents. Large volume of teaching material and large well organized teaching files, lecture and conference series, university affiliation. Good housing facilities, stipend from \$3900 to \$5400. Apply to Box 469, CMA Journal, 150 St. George St., Toronto 5, Ont.

**UNEXPECTED OPENING** for one pediatric resident, July 1, 1961. 100-bed children's hospital. Approved two year residency. Excellent program. Visiting professors from mainland universities. Salary \$200-250 plus maintenance. Fare from west coast. E.C.F.M.G. exam required. Write: Director of Medical Education, Kaulikeolani Children's Hospital, Honolulu, Hawaii.

**WANTED.**—Interns for 300-bed accredited hospital in St. Catharines, Ontario, with full laboratory and radiological services. Adequate time for study available and valuable clinical experience. Adequate salary plus full maintenance will be supplied, appointments to be effective July 1, 1961, for one year or 18 months. For further information write to Administrator, Hotel Dieu Hospital, St. Catharines, Ontario, Canada.

**WANTED.—SENIOR INTERN—anesthesia.** Salary \$2700. Apply to Superintendent, Sunnybrook Hospital, Toronto 12, Ontario.

## MEDICAL NEWS in Brief

(Continued from page 1265)

EFFECT OF VANADIUM  
SALTS IN THE INHIBITION  
OF CHOLESTEROL  
BIOSYNTHESIS

It has been known for some time that vanadium salts inhibit the biosynthesis of cholesterol in isolated liver homogenates. It has also been reported that the administration of vanadium salts to experimental animals or to human subjects is associated with a decrease in blood levels

of cholesterol. The mechanism by which vanadium salts inhibit cholesterol biosynthesis *in vitro* and lower blood levels of cholesterol *in vivo* has not been elucidated.

L. D. Wright, Lan-Fun Li, and R. Trager have recently reported in *Biochemical and Biophysical Research Communications* that liver homogenates preincubated with vanadium salts do not maintain a level of adenosine triphosphate (ATP). An adequate level of ATP is essential for the phosphorylation of intermediates prior to their utilization in cholesterol biosynthesis. These phosphorylated deri-

vatives (in the order in which they occur in cholesterol biosynthesis) are: mevalonic acid-5-phosphate, mevalonic acid-5-pyrophosphate, isopentenyl pyrophosphate, dimethyl allyl pyrophosphate, geranyl pyrophosphate, farnesyl pyrophosphate, and nerolidol pyrophosphate.

Whether or not the activity of vanadium salts in lowering blood levels of cholesterol is accomplished by an influence on tissue levels of ATP has not been established, but an active program of research exploring this possibility is underway. — Graduate School of Nutrition News, Cornell University.

Solve acute diarrheal  
and enteric problems  
without creating new problems



## FUROXONE

brand of furazolidone

LIQUID  
AND  
TABLETSantibacterial  
demulcent  
adsorptive

• Bactericidal perorally against a wide range of enteric bacteria 1, 2— including common pathogenic species and strains of *Escherichia*, *Salmonella* and *Staphylococcus* not adequately controlled by antibiotics and sulfonamides.

• Does not induce development of significant bacterial resistance, nor predispose to monilial or staphylococcal overgrowth.

• No toxicity reported.

• For patients of all ages (may be mixed with infant formulae... passes through a standard nursing nipple).

Available as Furoxone Liquid: bottles of 120, 240 cc. containing Furoxone, 50 mg. per 15 cc., with kaolin and pectin, pleasant orange-mint flavor.

Furoxone Tablets: 100 mg. scored, bottles of 20 and 100.

1. Ponce de Leon, E.: *Antibiotic Med. & Clin. Therapy* 4:816, 1957.

2. H. W. McFadden and M. M. Musselman: Personal communication to Eaton Laboratories.

NITROFURANS—a unique class of antibacterials

AUSTIN LABORATORIES LIMITED

BUELPH



CANADA

Registered user of the trade mark Furoxone of Norwich  
Pharmaceutical Company Ltd., Eaton Laboratories Division.

ACUTE HEALTH EFFECTS  
OF AIR POLLUTION

The harmful effects on public health of a marked increase in atmospheric pollution during prolonged periods of fog have been established beyond a shadow of doubt. The city of London, England, has experienced a series of lethal fogs, accompanied by relatively high levels of smoke and sulfur dioxide, and greatly increased mortality and illnesses over periods of four to five days.

Apparently, an important feature of the more recent London smog episodes has been in the rise in the death rate on the first day of the fog at a time before the atmospheric pollution has attained its maximum. This would suggest that many other smog visitations of shorter duration may be associated with a definite mortality which may not be large enough to become obvious through mortality statistics. The view has been expressed that in a London fog if the pollution exceeds the critical level of about four times the customary winter average, the resultant effect on public health will cause an immediate, marked increase in mortality. Thus far, only air-borne particulate matter (smoke) and sulfur dioxide have been measured on a systematic basis in the London atmosphere, but there is no doubt that many of the other common pollutants associated with fuel burning and industrial and transportation activities would also accumulate under the inversion blanket to correspondingly high levels.

In the United States, the most dramatic air pollution incident involving public health occurred during the five-day fog that enveloped Donora, Pa., on October 26 to 29, 1948. As a result of the accumulation of coal

(Continued on page 38)

# Tandearil<sup>®</sup> Geigy

## In Surgery

Modifies and relieves post-operative pain and swelling.

In conjunction with antibiotics, and drainage when necessary, controls the inflammation associated with surgical infections.

## In Medicine

Indicated in the wide range of diseases caused by acute and chronic non-specific inflammation.

Controls the symptoms of  
Arthritis

Periarticular Inflammation  
Vascular Inflammation

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## new non-hormonal anti- inflammatory agent

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In animals, Tandearil has demonstrated the ability to inhibit or suppress experimentally produced inflammation lesions.<sup>1</sup> Using the granuloma pouch technique of Selye in rats, Tandearil produced a marked inhibition of exudation and formation of inflammatory granulation tissue. In human beings, this property has been demonstrated in a broad range of indications in which inflammation plays a role. In contrast to other anti-inflammatory agents, Tandearil is not a proteolytic enzyme or corticosteroid and does not affect the pituitary adrenal axis.

For complete information on dosage, side effects and contra-indications, see the basic brochure or your Geigy representative.

## Availability

Tandearil, 1-phenyl-2-(p-hydroxyphenyl)-3, 5-dioxo-4-n-butyl pyrazolidine monohydrate, 100 mg light brown coated tablets. Bottles of 50 and 500.

1. Wilhelmi, G.: *Arzneim. Forsch.* 10:129-133, February 1960.



Geigy Pharmaceuticals  
Division of Geigy (Canada) Limited  
2626 Bates Road  
Montreal 26, Canada

**MEDICAL NEWS in brief***(Continued from page 32)*

smoke, sulfur dioxide, and other contamination under the heavy inversion layer, 5910 persons or 42.7% of the town population became ill and 20 died. A thorough study of this episode by the United States Public Health Service failed to disclose that any single pollutant could have caused these drastic effects on health, and it was concluded that the illnesses and deaths were due to a synergistic factor involving several contaminants whose joint action was

apparently much greater than the mere additive effect of each taken separately.

These air pollution disasters show many common features as to the meteorological conditions that led to the abnormal increase in contaminant concentrations and in the resultant symptoms and manifestations of the affected populations. The complaints of those who became ill included throat irritation, cough, shortness of breath, nausea, dyspnea, cyanosis, bronchospasm and vomiting. The majority of illnesses and fatal cases

were in persons who were elderly or had a history of pre-existing cardiopulmonary or respiratory conditions which might increase their susceptibility to atmospheric irritants.—M. Katz, *Occupational Health Review*, vol. 13, No. 1, 1961.

### ANESTHESIA AND MATERNAL MORTALITY

In its Report Number 4, published in the *Ontario Medical Review* (28: 106, 1961), the Maternal Welfare Committee of the Ontario Medical Association emphasizes that almost all maternal anesthesia deaths can be prevented by close attention to the following principles and procedures.

All obstetrical anesthesia should be considered as emergency anesthesia and as such should be undertaken when necessary facilities are available to meet any and every possible hazard.

The practice of applying pressure on the abdomen of an anesthetized patient in order to extricate the baby or the placenta should be avoided since it may also cause regurgitation.

If the patient should aspirate regurgitated material, gas anesthesia should not be re-started; local or epidural blocks should be used instead. If the latter are contra-indicated for any reason a clear tracheobronchial airway should be ensured before further inhalation anesthesia is administered.

If pulmonary edema develops it should be treated adequately with aminophylline and Solucortef. In attempting to maintain satisfactory blood pressure levels, flooding with intravenous fluids must be avoided.

Like many other aspects of medicine, anesthesia has become so complicated that in any area or community where a reasonably large number of deliveries are conducted, arrangements should be provided to have an anesthetist on 24-hour call at all times.

It is essential that hospitals constantly maintain all anesthesia equipment in proper working condition; such equipment includes not only gas machines but oxygen facilities, suction apparatus, instruments for bronchoscopy, cardiac restorative equipment and emergency drugs.

### FOURTH INTERNATIONAL CONGRESS OF ALLERGOLOGY

The Fourth International Congress of Allergology will be held at the Hotel Commodore, New York City,

Mrs. M. R., 75-year-old  
underweight patient:



Puts on 13 1/4 needed pounds  
in just 6 weeks;



gains 1" on right biceps;



forces mercury column 14 mm.  
higher in cuff-compression test  
of muscle strength;



feels better than she has  
in 2 years.

Photos used with permission  
of the patient.

## New Danabol converts protein to working weight in wasting or debilitated patients

Danabol is a new tissue-building agent with distinct advantages over previous compounds of this type.


By aiding the deposition, synthesis, and utilization of protein, Danabol affords these benefits in the underweight elderly patients with or without serious disease and in patients who are chronically ill or convalescent:

- Rebuilds tissue and improves appetite, thus promoting lean weight gain.
- Restores tone to weak, flabby musculature.
- Speeds healing of wounds; hastens postoperative recovery and convalescence from a variety of diseases.
- Strengthens skeletal structure; often relieves pain and increases mobility in osteoporosis.
- Improves general physical status; helps to revive a sense of well-being.

Economical, convenient to administer, and almost without virilizing effects, Danabol overcomes the disadvantages that have restricted use of tissue-building compounds in the past. Older patients, whose funds are often limited, will particularly welcome the low cost of Danabol therapy.

Complete information available on request.

SUPPLIED: Tablets, 5 mg. (pink, scored); bottles of 100 and 500.



## Danabol

(methandrostenolone CIBA)

**New, orally effective tissue builder**

---

**Converts protein to working weight  
in wasting or debilitated patients**

CIBA

October 15-20, 1961. It is anticipated that this will be a large and interesting meeting for all of those concerned with allergic diseases and related fields of immunology. At the main meetings, there will be simultaneous translations of all papers in English, French, German and Spanish. Prominent physicians and scientists, from all parts of the world, have been invited to take part in conferences, symposia and panel discussions. Among the subjects to be presented are: genetics in allergy; acquired tolerance; transplantation immunity; drug hypersensitivity; contact allergy; general mechanisms in allergy; mechanisms of antibody fixation; delayed hypersensitivity; auto-immune processes; steroid therapy; new methods in allergy.

All physicians registering are invited to present communications which will be grouped in various sections according to subject matter. An active program of entertainment is being arranged with several receptions, one at the Metropolitan Museum of Art, and a banquet. For the ladies, there will be a program of luncheons, fashion shows, and visits to the United Nations and other points of interest.

The registration fee for regular members will be \$45, for wives \$20. These registration fees will include the printed proceedings and admission to the receptions. The banquet will be charged separately. As the attendance is expected to be large, it is requested that persons interested obtain additional information from Dr. William B. Sherman, 60 East 58th Street, New York 22, New York.

#### SPECIAL FELLOWSHIP IN MEDICAL NEOPLASIA: MEMORIAL CENTER, NEW YORK

Memorial Center is a training centre affiliated with Cornell University Medical College. Specializing in cancer and allied diseases, it participates actively in teaching at both undergraduate and graduate levels. It has a fully approved residency program in internal medicine, and, in addition, offers special fellowships for study to a limited number of graduate physicians.

The scope and purposes of the Fellowship are: (1) to offer to physicians trained in internal medicine the opportunities available at Memorial Center to study the natural history,

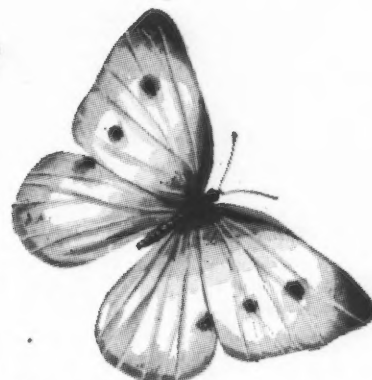
(Continued on page 40)



**RAPID RELAXATION**



**PEACEFUL SLEEP**



**REFRESHED AWAKENING**

**PLEXONAL**  **FORTE**<sup>®</sup>  
SLEEP GENTLY ANYWHERE

Plexonal Forte provides peaceful, restful and refreshing sleep for your patients. Plexonal Forte acts rapidly, evenly and without causing side-effects or after-effects. Can be used over a prolonged period of time without loss of effectiveness. Habituation has not been observed, and patients usually require smaller doses as they improve.

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Caffeine citrate ..... ½ gr.

### MEDICAL NEWS in brief

(Continued from page 39)

diagnosis, complications, pathogenesis and pathologic physiology, pathology and treatment of cancer, with particular emphasis on the leukemias, lymphomas and allied diseases; and (2) to undertake an active supervised clinical investigation of interest to the service and the Fellow in the field of medical neoplasia (non-surgical cancer and palliative therapy of patients with malignant tumours).

The Fellow will undertake the clinical or clinical and laboratory study of an approved or assigned problem under reasonable guidance and supervision. The study is to be carried out at Memorial Center under the aegis of the Lymphoma Service of the Department of Medicine. Available for clinical investigation are hospital records of 40 years, plus an active service consisting of approximately 40 beds in the Memorial Center, and two outpatient clinics in which an average of 75 patients are seen weekly. He will attend a weekly service teaching conference, and medical grand rounds. There will be periods of assignment to various surgical clinics and conferences, cancer chemotherapy, radiochemistry, radiophysics and radiotherapy. He will engage in the integrated study of the hematology and pathology of cancer, and will observe the role of the medical consultant to patients undergoing radical surgery for cancer. He will have a unique opportunity to see and study the management of large numbers of patients with lymphomas, leukemias and allied diseases.

Candidates must be graduates of recognized A.M.A.-approved medical schools, and must have completed or be in process of completing two years of postgraduate training in internal medicine in addition to one year of formal residency or its equivalent. Candidates must be of the highest integrity and moral character and have an expressed interest, both academic and clinical, in the study of malignant neoplastic diseases.

The salary stipend is \$6000 *per annum* without maintenance. The fellowship appointment is for one year normally beginning July 1, renewable for one or two years for select individuals who develop a special interest in some problem.

Applicants should apply in writing to: Henry D. Diamond, M.D., Chief, Lymphoma Service, Department of Medicine, Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N.Y.



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MONTREAL CANADA

## NEW FRENCH JOURNAL OF ALLERGY

Only recently off the press is the first issue of the *Revue Française d'Allergie*. The *Revue* will be published in the French language on a quarterly basis, in January, April, July and October. Devoted entirely to the field of allergy, this journal, the first of its kind to be published in France, will feature original articles dealing with basic scientific research and biological and clinical aspects of allergic phenomena. It will also provide the medium for publication of the transactions of the three general meetings of the French Society of Allergy, reports of meetings of the Society's local branches and announcements concerning international and European congresses dealing with this branch of medicine.

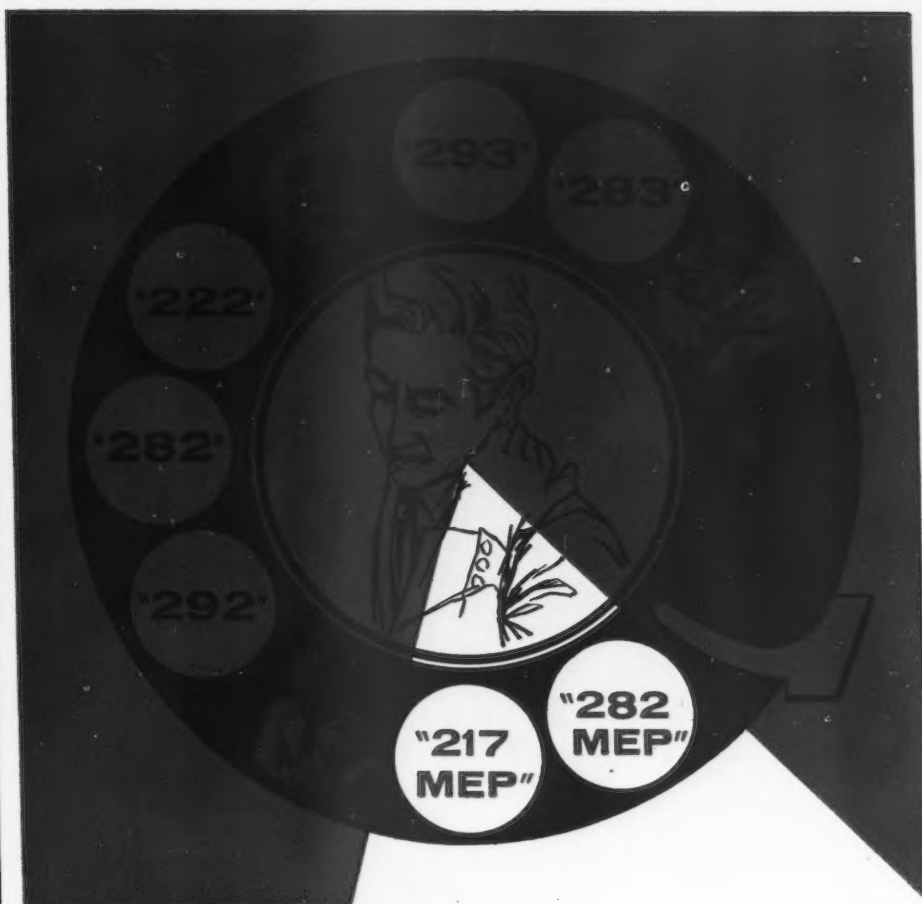
As pointed out by Vallery-Radot, in reviewing France's contributions to the study of allergy, it is particularly appropriate that such a publication should emanate from that country where, in 1902, Richet and Portier first demonstrated the phenomenon of anaphylactic shock, where Widal introduced the concept of allergic disease, where Bersredka pioneered in the principles of desensitization and where Halpern elucidated the antihistaminic properties of certain aniline derivatives, thereby opening the way to subsequent developments in antihistaminic therapy. Tribute is paid also to Pierre Blamoutier, current president of the French Society of Allergy, for his past contributions to this specialty and for his untiring efforts which contributed in no small part to the successful launching of the Society's new journal.

## GRANTS MADE BY CANADIAN LIFE INSURANCE OFFICERS ASSOCIATION

The Canadian Life Insurance Officers Association reports through its Public Health Committee that the life insurance companies doing business in Canada are co-operatively making grants for public health projects and medical research amounting to more than \$120,000 this year. This is in addition to the companies' individual contributions in excess of \$1 million to educational, health and welfare projects.

Organizations benefiting from the Association's grants are the Canadian Highway Safety Council; The Ontario

(Continued on page 43)



## NEW NUMBERS FOR RELIEF OF PAIN PLUS TENSION

These Frosst products permit your prescription of reliable, synergistic "217" analgesia formulations *plus* tension-relieving meprobamate—at usual "217" dosage—without exceeding a *safe total* dosage of meprobamate. In "282 MEP" the benefits of *codeine* are added for more severe pain in the presence of anxiety and/or muscle spasm.

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Acetylsalicylic acid .....	200 mg.	} PLUS Meprobamate .....	200 mg.
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Caffeine citrate .....	30 mg.		

### "282 MEP" TABLETS

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Dosage: "217 MEP" and "282 MEP"—One or two tablets every four to six hours as required.

Bottles of 12 and 100 tablets.

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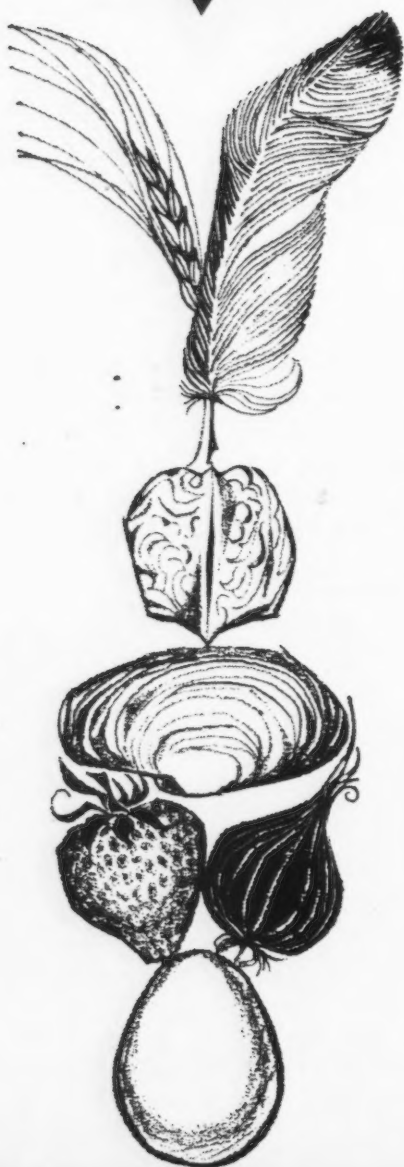
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"... hydroxyzine has been reported to possess considerable clinical value in the treatment of chronic urticaria."

J.H. Inogood et al., Applied Therapeutics, August 1960.

"... dramatic results in urticaria... Hydroxyzine combines antihistaminic properties in relieving allergic conditions with muscle-relaxing and tranquilizing effect in allaying the physical and mental stress reactions that accompany these disorders."

Santus, I.M.H. and Unger, L., F.A.C.A., Ann Allergy 18:172 (Feb.) 1960.

"... one of the most effective (tranquilizers) in chronic urticaria." "The relief of itching and hives is often dramatic."

Current Therapy, 1960 Edition, pp. 498.

"... (Atarax) which is also an antihistamine, seems to be the most effective in relieving the itchy patient..."

Anning, S.T., F.R.C.P.—Drug Treatment of Eczema, British Med. Journal, Nov. 21, 1959.

"A series of 151 allergic patients were treated with (hydroxyzine). The drug was effective in allergic rhinitis, urticaria, and pruritus of any allergic cause."

Grater, W.C., Postgraduate Medicine, November 1960.

"... in chronic urticaria... The relief of itching and hives is often dramatic."

Eisenberg, B.C., Management of Chronic Urticaria, J.A.M.A., Jan. 3, 1959, Vol. 169, No. 1.

"Pruritic symptoms were relieved by hydroxyzine in 70 of 77 patients with various common skin disorders."

Behling, R., Clinical Medicine, Aug. 1959.

"Overall results show that of seventy-five patients, seventy-two (96%) responded to treatment." "Hydroxyzine is an effective antipruritic and tranquilizing preparation with an exceptionally low order of toxicity."

Shapiro, I., Medical Times (Vol. 87, No. 12), December 1959.

"Hydroxyzine hydrochloride... Objective evaluation in 140 patients led to the conclusion that the use of hydroxyzine hydrochloride is valuable adjunctive therapy in the treatment of patients with dermatoses in which emotional tension is a factor."

Robinson, H.R., Jr., Robinson, R.C.V. and Strahan, J.F., Southern Medical Journal, Vol. 50, 1282-1287.

"In general the response of chronic urticaria to hydroxyzine hydrochloride has been very gratifying and useful."

Bottomley, H.W., M.D., F.A.C.P., Chronic Urticaria, The Winnipeg Clinic Quarterly—December 1960.

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**PFIZER CANADA**

## MEDICAL NEWS in brief

(Continued from page 41)

Society on Ageing; The Canadian Arthritis and Rheumatism Society; Montreal General Hospital; Queen's University; and St. Joseph's Hospital, Toronto.

The grants to the Canadian Highway Safety Council and the Ontario Society on Ageing are to provide general support for their current programs. The Canadian Arthritis and Rheumatism Society receives a grant for the second year for the purpose of assisting in the orderly development of its research program. The grant to the Montreal General Hospital is for a study on diabetes under the direction of Dr. G. E. Joron. The grant awarded Queen's University is for a study on hypertension under the direction of Dr. J. D. Hatcher. The grant to St. Joseph's Hospital, Toronto, is for a study of low back pain under the direction of Drs. G. F. Pennal and G. A. McDonald.

Since the inception of the Public Health Committee's activities, the Association has made grants and fellowships aggregating more than \$2 million.

## REFRESHER COURSES AT THE ROYAL VICTORIA HOSPITAL, MONTREAL

The Royal Victoria Hospital, Montreal, will conduct its twelfth annual refresher course for general practitioners from November 6 to 11 (inclusive), 1961. This will be followed by a course in clinical cardiology from November 13 to 16, 1961. The fee for the general practitioners' refresher course is \$75.00 and that for the course in clinical cardiology is \$50.00.

Applications to enrol in these courses should be submitted to the Post-Graduate Board, Royal Victoria Hospital, Montreal, P.Q.

## ANNUAL OTOLARYNGOLOGIC ASSEMBLY, UNIVERSITY OF ILLINOIS

The Department of Otolaryngology, University of Illinois College of Medicine, will offer an intensive post-graduate basic and clinical program under the direction of Dr. Emanuel M. Skolnik from September 23 to 30, 1961. This Assembly for practising otolaryngologists offers a compact program of one week of daytime and evening sessions. It is designed to bring to specialists a wide variety of

current advantages in management, therapy and philosophies. Review of basic morphologic features under the direction of Dr. Maurice F. Snitman and Dr. Frederic J. Pollock is also included, and will feature laboratory demonstrations, dissection and prosection, all augmented by visual aids.

Panel programs have been designed to bring out special features of otologic and reconstructive surgery and tumours of the head and neck. Luncheon chats are an important part of the daily program.

Interested physicians should write direct to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Ill.

## GROUP PSYCHOTHERAPY FOR EPILEPTICS

It is generally recognized that the health and adjustment of the epileptic is strongly influenced by his emotional response to his illness, the limitations that it imposes upon him and the attitudes of society, including his family, toward him. On the basis that epileptic subjects develop many disorders as a result of interpersonal experience it is logical to provide therapy for such disorders in a setting designed to encourage inter-action between those with emotional problems. Personality growth could also, conceivably, be fostered in such a setting by analysis of some aspects of the interaction and the emotions so aroused. Psychotherapy in a group may also provide much needed group support to facilitate the task of self-examination for epileptics who have, in many cases, long felt isolated from society and have erected a defensively hostile wall about themselves. Most epileptics in need of such therapy do not obtain it due to their lack of awareness, as well as to the limited availability of facilities for such treatment. Recognizing these needs, the Vancouver Epilepsy Centre has instituted a program whereby group psychotherapy will be provided for epileptic persons on a regular sessional basis (Slakov, I., B.C. M. J., 3: 84, 1961). The primary purpose of this program is the amelioration of emotional problems and behavioural difficulties. The relation between level of tension and number of seizures will be studied and the concept of a so-called "typical epileptic" psychopathology will be investigated.

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